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FLUOROHYDROCORTISONE AND CHLOROHYDROCORTISONE, HIGHLY POTENT DERIVATIVES OF COMPOUND F*

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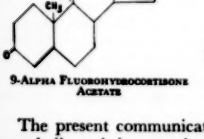
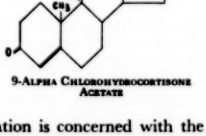
BOSTON

FRIED and Sabo,[1] while attempting to synthesize compound F from 11-epi-17-alpha-hydroxycorticosterone by way of a halogenated intermediate, found that the 9-alpha-chloro and fluoro derivatives of hydrocortisone were highly active in the assay of rat-liver glycogen for 11-oxygenated corticosteroids. Further studies in the rat by Borman, Singer and Numerof[2] have shown these compounds to have potent sodium-retaining activity as well. The structural formulas of these compounds are as follows:



9-ALPHA FLUOROHYDROCORTISONE ACETATE



9-ALPHA CHLOROHYDROCORTISONE ACETATE

The present communication is concerned with the metabolic and therapeutic effects of chlorohydrocortisone acetate and fluorohydrocortisone acetate in man. Preliminary studies indicate that whereas the actions of chlorohydrocortisone and fluorohydrocortisone are qualitatively similar to those of hydrocortisone, the intensity of effect is considerably enhanced and the duration of action is markedly prolonged. Of the two, fluorohydrocortisone is the more potent.

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METHODS

The metabolic studies were carried out on the metabolic ward of the Peter Bent Brigham Hospital.

The 17-hydroxycorticoids were determined by the method of Reddy, Jenkins and Thorn.[3] The 17-ketosteroids were determined by a modification of the method of Drekter et al.[4] whereby the colorimetry was performed as in the procedure of Holtorff and Koch.[5] Chemical determinations on blood and urine and eosinophil counts were carried out by methods previously described.[6]

METABOLIC STUDIES

The comparative effects of the acetates of fluorohydrocortisone, chlorohydrocortisone and hydrocortisone** on the excretion of sodium, potassium and glucose in the urine of a sixty-three-year-old man with Addison's disease are shown in Figure 1. During the control periods, the patient received cortisone acetate, 25 mg. a day by mouth. On the test days the cortisone was replaced by 25 mg. of one of the compounds listed above given in a single dose by mouth. The patient was allowed to come into balance again on cortisone acetate before the next test compound was administered. Figure 1 demonstrates that hydrocortisone produced little change over that observed with cortisone. Chlorohydrocortisone and fluorohydrocortisone, however, caused a marked fall in urinary sodium and a rise in urinary potassium and glucose, the effects being more profound with the latter compound. The persistence of intense sodium retention on the day after fluorohydrocortisone administration was particularly noteworthy. Fluorohydrocortisone and, to a lesser degree, chlorohydrocortisone, produced a greater and more prolonged eosinopenia (Fig. 2) than that seen with either cortisone or hydrocortisone.

In an attempt to quantitate the relative activities of the acetates of hydrocortisone, desoxycorticosterone, chlorohydrocortisone and fluorohydrocortisone on

**The hydrocortisone derivatives were kindly provided by Drs. Henry A. Strade and Lawrence B. Hobson, of the Squibb Institute for Medical Research.

sodium and potassium excretion, the compounds were administered to a thirty-five-year-old woman with Addison's disease who was being maintained in balance

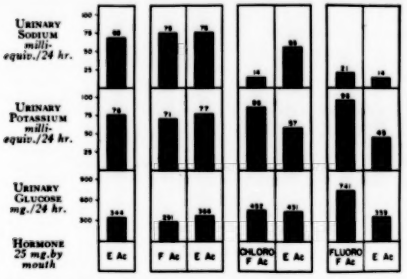

FIGURE 1. *Effects of the Acetates of Hydrocortisone, Chlorohydrocortisone and Fluorohydrocortisone on the Urinary Sodium, Potassium and Glucose Excretion in H. F., a Sixty-Three-Year-Old Man with Addison's Disease Maintained on a Constant Diet (Providing 104 Milliequiv. of Sodium and 87 Milliequiv. of Potassium per Day).*

on a constant diet. The compounds were administered as single oral doses except for the desoxycorti-

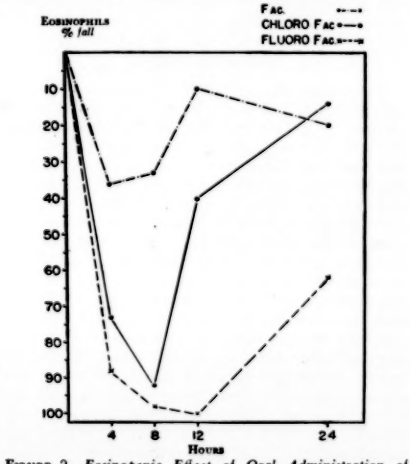

FIGURE 2. *Eosinopenic Effect of Oral Administration of 25 Mg. of Hydrocortisone, Chlorohydrocortisone and Fluorohydrocortisone in H. F., a Sixty-Three-Year-Old Man with Addison's Disease.*

costerone acetate, which was given by a single intramuscular injection. After the administration of each compound, the patient was allowed to come again into metabolic balance before the next substance was given. This experiment (Fig. 3) showed that 6 mg. of chlorohydrocortisone, 2 mg. of desoxycorticosterone, and 0.5 mg. of fluorohydrocortisone produced almost identical changes in sodium and potassium excretion. All three compounds displayed marked potency as compared to 25 mg. of hydrocortisone acetate given as a single oral dose.

In view of the recent discovery of aldosterone (electrocortin), a potent salt-retaining hormone of the adrenal cortex, it was of interest to compare the effect of this hormone on sodium and potassium excretion with that of fluorohydrocortisone free alcohol.* In a thirty-seven-year-old man with Addison's disease maintained in balance on a constant diet, each of these substances was administered intravenously in a dose of 200 microgm. in 250 cc. of 5 per cent dextrose in water over a four-hour period. The results of this study are presented in Figure 4. It can be seen that the effect of fluorohydrocortisone and aldosterone

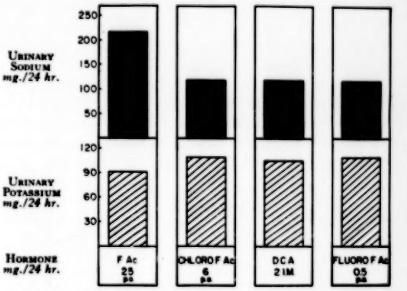

FIGURE 3. *Effects of the Acetates of Desoxycorticosterone, Hydrocortisone, Chlorohydrocortisone and Fluorohydrocortisone on Urinary Sodium and Potassium in M. McG., a Thirty-Five-Year-Old Woman with Addison's Disease Maintained on a Constant Diet (Providing 194 Milliequiv. of Sodium and 97 Milliequiv. of Potassium per Day).*

were practically identical during the four-hour infusion period. During the subsequent six hours and the overnight period, however, a prolonged effect of fluorohydrocortisone was observed, in contrast to the relatively rapid escape noted with aldosterone.

In a subject with normal adrenal function the substitution of 1 mg. of aldosterone as a single daily dose by mouth for 1 mg. of fluorohydrocortisone acetate similarly administered resulted in a small increase in sodium excretion and a small decrease in potassium excretion, suggesting that under these circumstances the aldosterone was slightly less effective than the equivalent quantity of fluorohydrocortisone (Fig. 5). It did not appear that the difference in potency was related solely to the fact that the acetate of fluorohydrocortisone was used in these studies as compared to the free form of aldosterone since fractionation of the urine specimens revealed less sodium retention in the first twelve-hour period after the administration

*Aldosterone was kindly supplied by Dr. Thaddeus Reichstein, of the University of Basle, and Dr. Robert Gaunt, of Ciba Pharmaceutical Products, Incorporated.

of aldosterone. Furthermore, the fluorohydrocortisone had a more prolonged effect than the aldosterone in the previous study (Fig. 4) in which the free form of each compound was used intravenously.

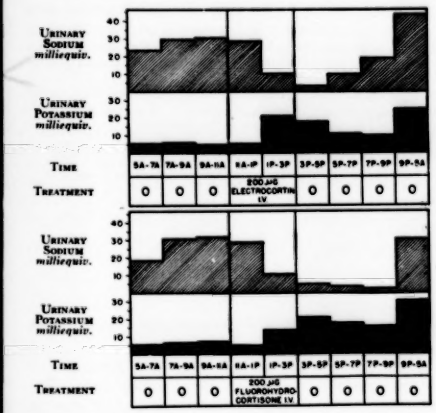

FIGURE 4. *Effects of Intravenously Administered Electrocortin and Fluorohydrocortisone on the Urinary Excretion of Sodium and Potassium in W. G., a Thirty-Seven-Year-Old Man with Addison's Disease Maintained on a Constant Diet (Providing 167 Milliequiv. of Sodium and 118 Milliequiv. of Potassium per Day).*

In an attempt to compare the relative potentiation of mineralocorticoid and glucocorticoid activity resulting from the insertion of a fluorine atom at the 9-alpha position of hydrocortisone, a twenty-five-year-old normal male subject on a constant diet was given an intravenous infusion of 100 mg. of hydrocortisone free alcohol in 500 cc. of physiologic saline solution over an eight-hour period under fasting conditions. Blood was taken at two-hour intervals for the determination of eosinophils and glucose. Sodium, potassium and uric acid determinations were made on urine specimens collected every two hours during the period of infusion. Two days later, the experiment was repeated, 2 mg. of fluorohydrocortisone free alcohol being substituted for the hydrocortisone. The results are shown in Table 1. It is clear that the effect of 2 mg. of fluorohydrocortisone on sodium excretion is equal to that observed with 100 mg. of hydrocortisone. The effect of 100 mg. of hydrocortisone was definitely greater than that of 2 mg. of fluorohydrocortisone on the level of circulating eosinophils and the level of blood glucose and uric acid excretion. Subsequent studies indicate that 1 mg. of fluorohydrocortisone is equivalent to approximately 20 mg. of cortisone in its eosinopenic, anti-inflammatory and organic metabolic action.

In view of the marked sodium-retaining potency of fluorohydrocortisone, it was considered desirable to investigate the comparative effects of relatively large doses of this steroid in subjects with intact adrenal glands. Such a study was carried out in subject C.E. (Fig. 6), in whom the effect of 25 mg. of fluorohydrocortisone daily was compared with that of 5 mg. daily. Of particular interest was the finding that the larger dose of fluorohydrocortisone did not cause a significantly greater sodium retention. Furthermore, an escape in sodium excretion occurred after three days. With the large dose of fluorohydrocortisone, however, maximum sodium retention was observed in the first twenty-four hours, whereas the same degree of retention was not attained until forty-eight hours at the 5-mg. level.

A study has been made to determine the minimum quantity of fluorohydrocortisone that is capable of producing a detectable inhibition of pituitary and adrenal secretion in a male subject with normal adrenal function (Fig. 7). After the administration of 1 mg. of fluorohydrocortisone acetate daily by mouth, the 17-hydroxycorticoids fell promptly from an average control level of 8.7 mg. to a level of approximately 2.5 mg. a day. A decrease in 17-ketosteroid excretion was also observed; however, the response was less striking. Standardized intravenous ACTH tests carried out during the control period and later while the subject was receiving 1 mg. of fluorohydrocorti-

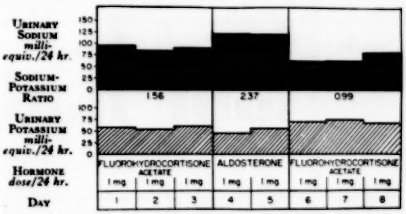

FIGURE 5. *Effect of the Substitution of 1 Mg. of Aldosterone, Administered by Mouth As a Single Dose to R. A., a Thirty-Eight-Year-Old Man with a Spinal-Cord Tumor. This patient with normal adrenal function was maintained in balance on a constant diet (providing 86 milliequiv. of sodium and 78 milliequiv. of potassium), with 1 mg. of fluorohydrocortisone daily by mouth.*

sone indicated a decreased adrenocortical responsiveness (Fig. 7). Additional studies showed that 1 mg. of fluorohydrocortisone acetate appeared to be close to the minimum level at which a decrease in adrenocortical secretory activity might be demonstrated in a single dose by mouth daily.

Clinical Applications

Substitution Therapy in Patients with Adrenal Insufficiency

The use of fluorohydrocortisone acetate as the sole maintenance therapy in Addison's disease is demon-

strated in Figure 8. The patient, a thirty-seven-year-old man, was admitted to the hospital in *severe Addisonian crisis.* At the time of admission, the patient weighed 54 kg., and the heart size was 15 per cent below normal. There was great improvement within hours of the first dose of 6.25 mg. of fluorohydrocortisone by mouth. After ten days of treatment at this level, the patient felt quite well in spite of excessive fluid and salt retention manifested by edema, pleural effusion, cardiac enlargement, a weight gain of 12 kg. and a 40 per cent increase in exchangeable body sodium.* The dose of the hormone was first reduced to 1 mg., then to 0.5 mg. and finally to 0.25 mg., given as a single oral dose daily. On this regimen the patient continued to improve clinically, lost his excess fluid, but gained a further 2 kg. in weight, which was associated with a 30 per cent increase in exchangeable body potassium; the heart decreased in size. The previously impaired capacity to excrete an ingested water load returned to normal. For the past six months this patient has been maintained in excellent condition with 0.25 mg. of fluorohydrocortisone acetate taken once daily by mouth. On this program he is able to carry on full-time activity as a skilled laborer. Furthermore, ACTH administered intravenously has failed to elicit any adrenocortical response. It is of interest that on this small dose of fluorohydrocortisone acetate no 17-hydroxycorticoid material can be measured in the urine by the Porter–Silber reaction. In contrast to this patient, most of the patients being maintained on 9-alpha fluorohydrocortisone require approximately 2.5 mg. of supplementary cortisone to achieve a maximum sense of well-being.

A forty-year-old woman with Addison's disease, previously maintained on 37.5 mg. of cortisone acetate daily by mouth and 37.5 mg. of desoxycorticosterone trimethylacetate by intramuscular injection every four weeks, is now being maintained satisfac-

TABLE 1. *Effects of Hydrocortisone (100 Mg. over an Eight-Hour Period) and Fluorohydrocortisone (2 Mg. over an Eight-Hour Period) on the Blood Eosinophil Level, Blood Glucose Level and Urinary Sodium, Potassium and Uric Acid Excretion in a Normal Male Subject Maintained on a Constant Diet.**

TIME	SODIUM EXCRETION		POTASSIUM EXCRETION		BLOOD EOSINOPHIL LEVEL		BLOOD GLUCOSE LEVEL		URIC ACID EXCRETION	
	ON FLUOROHYDROCORTISONE	ON HYDROCORTISONE	ON FLUOROHYDROCORTISONE	ON HYDROCORTISONE	ON FLUOROHYDROCORTISONE	ON HYDROCORTISONE	ON FLUOROHYDROCORTISONE	ON HYDROCORTISONE	ON FLUOROHYDROCORTISONE	ON HYDROCORTISONE
	milliequiv./2 hr.	*milliequiv./2 hr.*	*milliequiv./2 hr.*	*milliequiv./2 hr.*	*per cu. mm.*	*per cu. mm.*	*mg./100 cc.*	*mg./100 cc.*	*mg./2 hr.*	*mg./2 hr.*
7 a.m.	61	77	12	11	216	200	69	66	120	139
9 a.m.	26	42	19	11	156	106	71	79	110	113
11 a.m.	14	29	19	19	144	38	73	82	103	140
1 p.m.	16	23	15	20	119	3	79	99	103	149
3 p.m.					119	6	77	93		

*Diet contained 324 gm. of carbohydrates, 156 gm. of protein, 159 gm. of fat, 204 milliequiv. of sodium and 115 milliequiv. of potassium. Steroids infused intravenously between 7 a.m. and 3 p.m.

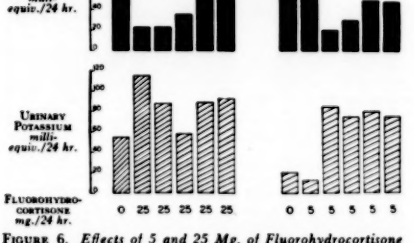
URINARY SODIUM milli-equiv./24 hr.
URINARY POTASSIUM milli-equiv./24 hr.
FLUOROHYDROCORTISONE mg./24 hr.
0 25 25 25 25 25
0 5 5 5 5 5

FIGURE 6. *Effects of 5 and 25 Mg. of Fluorohydrocortisone in Single Doses by Mouth, on the Urinary Excretion of Sodium and Potassium in a Twenty-Year-Old Woman with Infertility on a Constant Diet (Providing 114 Milliequiv. of Sodium and 93 Milliequiv. of Potassium).*

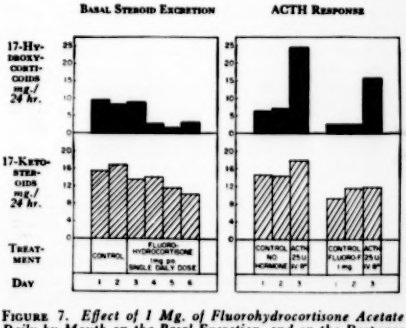

FIGURE 7. *Effect of 1 Mg. of Fluorohydrocortisone Acetate Daily by Mouth on the Basal Excretion, and on the Response to ACTH, of Urinary 17-Hydroxycorticoids in a Forty-Year-Old Man with a Spinal-Cord Tumor but with Normal Adrenal Function.*

*We are indebted to Dr. Walter L. Arons for performing the determinations of exchangeable body sodium and potassium reported in this paper.

torily on chlorohydrocortisone acetate alone at a dose of 7 mg. a day by mouth.

The fact that small quantities of fluorohydrocortisone are very effective in maintaining patients with Addison's disease in excellent condition and that under these circumstances little or no interfering steroid material appears in the urine facilitates the administration of ACTH for diagnostic purposes, since it is possible to follow carefully the urinary steroid response for several days, and thus to differentiate primary and secondary adrenocortical insufficiency without in any way compromising the clinical condition of the patient. Hence, under these circumstances, it is not necessary to withhold substitution therapy while the diagnosis is being established.

A further use for fluorohydrocortisone is in the evaluation of adrenocortical function in patients on long-maintained cortisone or hydrocortisone therapy. Since negligible quantities of 17-hydroxycorticoids are found in the urine after the administration of effective doses of fluorohydrocortisone, it is possible to substitute this compound for cortisone or hydrocortisone (in the ratio of approximately 1 mg. of fluorohydrocortisone to 20 mg. of cortisone or hydrocortisone) while standard ACTH tests are being carried out. Thus, the dangers inherent in the sudden withdrawal of corticoid therapy are avoided, and a definitive answer regarding adrenocortical reserve can be obtained. As an illustration, studies have been carried out on a patient suffering from severe gouty arthritis (Fig 9). In this case 3 and then 2 mg. of fluorohydrocortisone as a single oral dose were substituted for 50 mg. of cortisone, which the patient has been receiving daily for approximately four years. It is of interest that metabolic transformation products measurable by the Porter–Silber reaction were excreted for approximately forty-eight hours after the last oral dose of cortisone acetate (50 mg. per day). The small quantity of 17-hydroxycorticoids secreted in response to ACTH might not have appeared significant

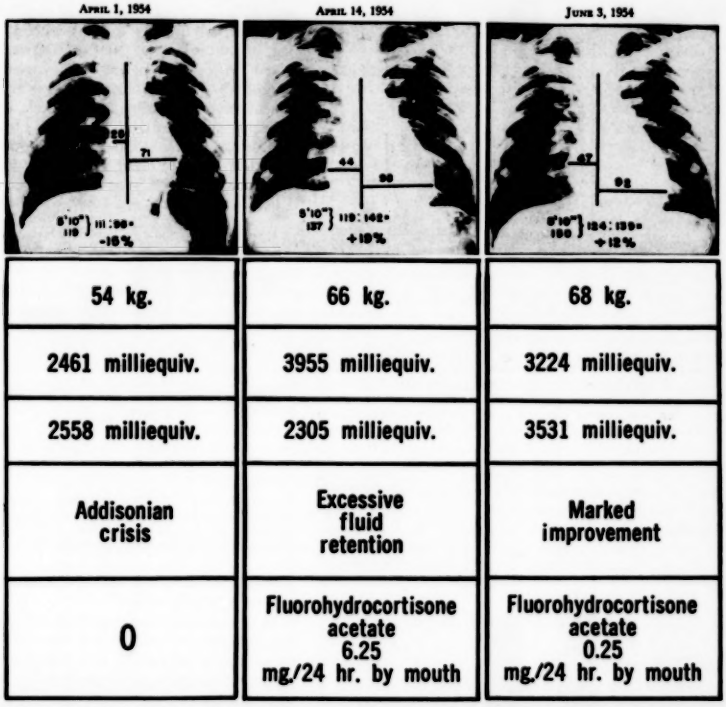

Figure 8. *Effects of Fluorohydrocortisone Acetate Therapy in a Thirty-Seven-Year-Old Man with Addison's Disease.*

when superimposed on the higher basal level attained with 50 mg. of cortisone acetate orally.

Inhibition of Endogenous Adrenocortical Secretion

Diagnostic applications. Fluorohydrocortisone possesses several advantages over cortisone as a diagnostic agent in the differentiation of the origin and type of tissue responsible for hyperadrenocorticism. The prolonged effectiveness that follows oral administration and the marked potency of the compound eliminate the need for parenteral administration and minimize the confusion introduced when one attempts to interpret the change in urinary 17-ketosteroid and 17-hydroxycorticoid levels after adrenocortical inhibition with large doses of cortisone or hydrocortisone. An example of the inhibitory effect of fluorohydrocortisone in a patient with the adrenogenital syndrome is presented in Figure 10. In this patient the 17-ketosteroids, which ranged from 23 to 26 mg. per day, fell to 7 mg. per day after five days of 10 mg. of fluorohydrocortisone acetate given as a single daily dose by mouth. After ten days of treatment at this dosage the urinary 17-ketosteroid level fell to 4 mg. a day. This low level has now been maintained for a period of four months with a dose of only 2 mg. of steroid a day. No untoward effects have been noted during this period. The prompt response to fluorohydrocortisone acetate suggests that in this case the hormonal disturbance was most probably due to bilateral adrenocortical hyperplasia.[7] In 5 other female patients with hirsutism and increased urinary 17-ketosteroid excretion a dose of fluorohydrocortisone as low as 1 or 2 mg. a day, given by mouth, was sufficient to maintain the 17-ketosteroid excretion at normal levels or below.

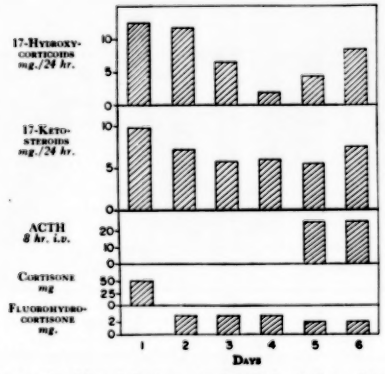

FIGURE 9. *Adrenal Response to ACTH in A. L., a Sixty-Two-Year-Old Man with Chronic Gouty Arthritis after Four Years of Uninterrupted Cortisone Therapy (50 Mg. Daily by Mouth).*

After the first control day the patient was maintained on 3 and then on 2 mg. of fluorohydrocortisone acetate by mouth.

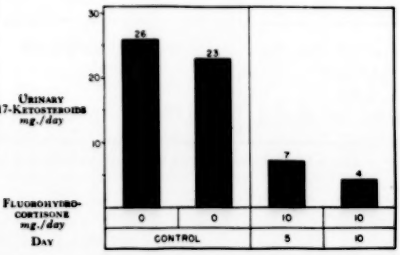

FIGURE 10. *Inhibiting Effect of Oral Administration of Fluorohydrocortisone Acetate on the Adrenal Cortex of a Twenty-Six-Year-Old Woman with the Adrenogenital Syndrome (Bilateral Hyperplasia).*

In a patient presenting evidence of adrenocortical hyperfunction of the mixed type it was possible to demonstrate inhibition of endogenous 17-hydroxycorticoid, as well as 17-ketosteroid, secretion (Fig. 11). In this patient a daily dose of 5 mg. of fluorohydrocortisone for ten days appreciably lowered the excretion of both 17-hydroxycorticoids and 17-ketosteroids. Increasing the fluorohydrocortisone to 25 mg. resulted in a further decrease in 17-ketosteroids and no further significant change in 17-hydroxycorticoid excretion. This might be explained by the fact that the relatively large quantities of fluorohydrocortisone required account for approximately 4 or 5 mg. of 17-hydroxycorticoid material, as suggested by the immediate reduction in 17-hydroxycorticoid excretion that followed the discontinuance of fluorohydrocortisone. At operation bilateral adrenal hyperplasia (adrenal weight, 24 gm.) was confirmed.

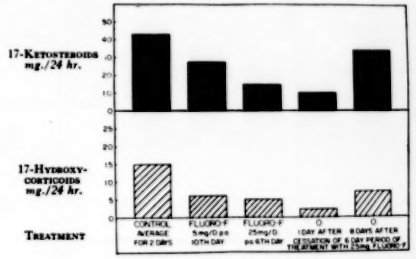
17-Ketosteroids mg./24 hr.
17-Hydroxy-corticoids mg./24 hr.
Treatment
Control Average for 2 days
Fluoro-F 5 mg./D p.o. 10th day
Fluoro-F 25 mg./D. p.o. 6th day
1 day after
8 days after cessation of 6 day period of treatment with 25 mg. Fluoro-F

FIGURE 11. *Effects of 5 and 25 Mg. of Fluorohydrocortisone Acetate by Mouth on the Urinary Excretion of 17-Ketosteroids and 17-Hydroxycorticoids in P. T., a Twenty-Eight-Year-Old Woman with Adrenocortical Hyperfunction.*

It is of considerable practical significance that long-

term suppression of the adrenal cortex may be maintained by the daily administration of a single oral dose of fluorohydrocortisone. It is to be emphasized, however, that, because of the intense mineralocorticoid activity of fluorohydrocortisone, potassium chloride should be administered along with this compound and that a restriction of sodium intake should be considered, to prevent excessive salt and water retention.

The possible advantages or disadvantages of fluorohydrocortisone as an anti-inflammatory agent have not been fully explored. However, it appears that the clinical effects of 1 mg. of fluorohydrocortisone are similar to those of 15 to 25 mg. of cortisone or hydrocortisone. Whether or not the enhanced sodium-retaining effect limits its usefulness depends on the dosage required and the individual susceptibility of the patient to salt retention.

Summary and Conclusions

Metabolic and therapeutic studies with chlorohydrocortisone and fluorohydrocortisone indicate that the insertion of a chlorine or fluorine atom at the 9-alpha position of hydrocortisone greatly potentiates both the metabolic activity and the duration of action of the parent compound. Of the two derivatives, fluorohydrocortisone is the more potent. Preliminary studies indicate that the ratio of mineralocorticoid to glucocorticoid activity is somewhat greater for fluorohydrocortisone than for hydrocortisone. Both chlorohydrocortisone and fluorohydrocortisone have been successfully employed as the sole maintenance therapy in patients with Addison's disease. Furthermore, satisfactory inhibition of the adrenal cortex has been achieved with doses of 1 or 2 mg. of fluorohydrocortisone by mouth a day in normal subjects and in female patients with the adrenogenital syndrome. In a patient with a mixed clinical picture due to bilateral adrenal hyperplasia, adrenal inhibition was demonstrated at dosage levels of 5 and 25 mg. of fluorohydrocortisone daily.

The substitution of fluorohydrocortisone for cortisone or hydrocortisone in patients on long-term corticoid therapy permits the evaluation of adrenocortical function with standardized ACTH tests without the necessity for discontinuing effective therapy with adrenal hormones.

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ULCERATIVE COLITIS*

Follow-up Studies

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BOSTON

SINCE 1915 a continuing interest in ulcerative colitis at the Massachusetts General Hospital has been shown by a series of staff members, both medical and surgical. The years have witnessed an evolution in operative management from simple appendicostomy to primary total colectomy and ileostomy at one stage. Clinical studies published in the past have dealt with the proper timing and type of operation, appraisal of the ileostomy nuisance and evaluation of the complications of ileostomy.[1-3]

Separation of patients into medical and surgical groups has been a matter of custom to conform to the necessity of so dividing clinical responsibilities, and has inevitably resulted in a similar segmentation in the study of the disease. Since this has seemed to us a situation to be avoided, particularly in ulcerative colitis, in which "team" management is so important, we have undertaken to study an entire group of patients, however treated, admitted to the hospital during a given period.

The current report is on the status of patients with whom contact was established not less than ten years after their initial treatment at the Massachusetts General Hospital. Special consideration is also given to the problem of carcinoma of the colon in these patients, and to the frequency of small-bowel obstruction after ileostomy or colectomy.

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Material

Of 713 patients treated for ulcerative colitis at the Massachusetts General Hospital from 1915 through 1949, 483 (67.8 per cent) were seen before 1943. It

is with this group that we are concerned. Three hundred and forty-three (71 per cent) of these were traced for ten years or until death, and the remainder were lost to follow-up study.

Before a patient was classified as untraced, letters and telephone calls had been sent to him, his family and friends, and the referring physician. If this maneuver was nonproductive, the death files at the State House were inspected to see whether we could prove that death had occurred. In view of the interval between the first year of the study and the present — a maximum of thirty-eight years — it is not surprising that many patients could not be found.

TABLE 1. *Fate of Traced Patients.*

FATE OF PATIENT		NO. OF PATIENTS
Living		155(45.3%)
Dead		188(54.7%)
Of ulcerative colitis, without operation	46	
Of ulcerative colitis, with operation	107	
Of other causes, without operation	28	
Of other causes, with operation	7	

In this follow-up study we are indebted to a large number of the members of the staff of the Massachusetts General Hospital for allowing us to include their private patients and for having been co-operative in providing data on them.

RESULTS

Survival

Of the 343 patients accounted for, 155 (45.3 per cent) were living and 188 (54.7 per cent) were dead at the time of follow-up study (Table 1). Ulcerative colitis was responsible for 153 (81.2 per cent) of the 188 deaths by means of peritonitis, hemorrhage, "toxicity," carcinoma of the colon or, in the early days, "bronchopneumonia." The other 35 patients died of unrelated causes.

TABLE 2. *Results of Nonoperative Treatment.*

RESULT	PATIENTS TRACED	TOTAL PATIENTS
Death without operation	74(19.1%)	74(15.3%)
Eventual operation	232(60.0%)	232(48.0%)
Survival without operation	81(20.9%)	81(16.7%)
Not known	—	96(19.8%)
Totals	387	483

Results of Nonoperative Treatment

When new patients with ulcerative colitis are seen it is hoped that the disease can be controlled without ileostomy. Thus, at the onset of therapy, all patients except those presenting an outspoken surgical emergency are treated by nonoperative means. It was possible to evaluate the result of nonoperative treatment in 387 patients, a group made up of the 343 patients who died or were followed for ten years, in addition to 44 patients who required operations and then were "lost" to follow-up study (Table 2). Of this group 74 (19.1 per cent) died without operation (46 of them from ulcerative colitis), 81 (20.9 per cent) are living without operation, and 232 (60 per cent) came sooner or later to operation. The figure of 20.9 per cent for patients living without operation means little since it is probable that many of the 96 untraced patients also did well, the disease having been mild in 67 per cent of them when they were under our care. Thus, the figure of 20.9 per cent who avoided operation might actually be almost as high as 50 per cent. Obviously, the disease was more severe in the patients who were operated on or who died of ulcerative colitis.

Duration of Disease before Surgery or Death

The question of how long it may take ulcerative colitis to necessitate operation or to cause death was examined (Table 3). The disease varies widely from a severe fulminating type, exemplified by the 11 deaths and 35 operations noted in the first three months of its course, to a more chronic form marked by exacerbations and remissions. The majority of patients who eventually succumbed or required surgery did so within three years of onset (58 per cent for each group).

TABLE 3. *Duration of Disease before Death or Operation.**

DURATION	BEFORE DEATH WITHOUT OPERATION	BEFORE OPERATION
Less than 3 mo.	11(23.9%)	35(17.9%)
3-12 mo.	6(13.1%)	29(14.7%)
1-3 yr.	10(21.8%)	50(25.6%)
3-5 yr.	5(10.7%)	20(10.2%)
More than 5 yr.	14(30.5%)	62(31.6%)
	46	196

*Duration could not be established in 36 of the earlier cases.

Surgical Indications and Mortality

In the period before 1930 operation for ulcerative colitis carried a mortality of over 50 per cent. From 1930 through 1939 the mortality after simple ileostomy was 26.8 per cent. This is explained, partially at least, by the indications for surgery, which, from 1915 through 1942, were emergency* or urgent in 80.4 per cent of the cases. Subsequently, the mortality of ileostomy fell to 12.5 per cent in 1940 through 1949 and 7.7 per cent (or 3 deaths in 39 patients) from

*"Emergency" ileostomy indicates that the disease was completely uncontrolled by nonoperative therapy. "Urgent" operation is undertaken with the disease partially controlled but with the patient in less than optimum condition.

1950 through 1953. The indications for surgery were emergency or urgent in only 66.3 per cent of the cases from 1943 through 1949.

Status of Survivors

The results of treatment with or without operation indicate that those surviving now have the disease under control and are useful citizens (Table 4). This is true of 79 per cent of those who were not and 94.5 per cent of those who were operated on.

Frequency of Cancer

In our study we found 31 patients with ulcerative colitis in whom cancer developed, 28 having been seen at the Massachusetts General Hospital before 1943. The number of patients who lived ten or more years after the onset of ulcerative colitis and who did not have colectomy before ten years of the disease had elapsed is 319. Thus, of 319 candidates for the development of carcinoma of the colon, 28 did contract it — a rate of 8.8 per cent. The true figure is higher since here we have assumed that all the patients not followed had no cancer and that they lived for ten years or more. If we calculated this percentage on the basis of cases of carcinoma among our followed patients whose colons had not been removed, the incidence would be 18.1 per cent. It is of interest that 20 of the 31 cases were discovered between 1943 and 1953 and only 11 in the period 1915-1942. In other words, two thirds occurred in a period during which only a third of the total cases of ulcerative colitis were observed.

The locations of the carcinomas were spread evenly, with 7 in the ascending, 4 in the transverse, and 9 in the descending colon, 5 in the rectum, and the others not accurately located. In 2 patients a rectal carcinoma was found unexpectedly in the specimen after a combined abdominoperineal resection. One of them, who had a Grade 2 lesion, has survived for nine years, whereas the other died of recurrent carcinoma. In 4 cases ileostomy had been performed two to fifteen years before cancer developed (1 patient survived). Two patients were found to have multiple separate carcinomas of the colon.

TABLE 4. *Status of Living Patients.*

STATUS	PATIENTS WITHOUT OPERATION	PATIENTS WITH OPERATION
Disabled	2(2.5%)	1(1.4%)
Partially disabled	15(18.5%)	3(4.1%)
Well	64(79.0%)	70(94.5%)
Totals	81	74

The ages ranged from fourteen to sixty-four, and the duration of ulcerative colitis from three to forty-five years, with an average of ten and seven-tenths years. Only 5 patients had had ulcerative colitis for less than eight years (three, five, five, six and seven years). Nine had had severe attacks of active ulcerative colitis, and the rest had had chronic disease of varying intensity, 6 who were never sick enough to enter the hospital previously being carried as outpatients. In 13 there was evidence of pseudopolyps by either x-ray or pathological study.

Seven patients were alive at the time of this study, 2 of whom have lived for more than five years. One patient is alive eight years after a colectomy on the right for carcinoma of the cecum. Since she refused ileostomy, colectomy was done at some considerable risk of breakdown of the anastomosis. She is currently not symptom free, owing to the remaining colitis. The other patient, already mentioned, is alive nine years after proctosigmoidectomy at which the pathologist found a clinically unsuspected carcinoma.

Frequency of Intestinal Obstruction

The later course of patients treated by operation is frequently marred by the development of small-bowel obstruction. In our survey there were 26 admissions for unquestioned small-bowel obstruction occurring in 18 patients, 4 having 2 to 5 such episodes. By 1949, 139 patients with colectomies had survived operation and thereby became candidates for obstruction as well as the patients with ileostomy alone. It is of interest that all the patients had their first attack within a year of one of the stages of their operations for ulcerative colitis except 1, who went two years between operation and obstruction.

TABLE 5. *Small-Bowel Obstruction.*

PREVIOUS SURGERY	PATIENTS WITH VOLVULUS CAUSING OBSTRUCTION	PATIENTS WITH ADHESIONS CAUSING OBSTRUCTION	CAUSE OF OBSTRUCTION NOT KNOWN
Ileostomy only	2	0	1
Subtotal colectomy	2	7	4
Total colectomy	6	4	0
Totals	10	11	5

Four patients died of obstruction; 3 had no surgery for it. Two of these 3 had weathered obstruction in the past by means of intubation, which presumably led to the expectation that similar handling would be successful again.

Twenty-one of the 26 cases of obstruction were treated by surgery. In 10 the cause was found to be a volvulus around the ileostomy, and in 11 adhesions were at fault (Table 5).

DISCUSSION

A follow-up study of this nature has three weaknesses: the period considered was under the influence of changing and outmoded therapies so that the mortality cited was much higher than that observed now; not all patients could be followed; and the patients followed have not been studied by sigmoid-

oscopy and barium enema. A more detailed investigation of the third point is contemplated. All three considerations, although they limit the inferences to be drawn from study, do not prevent certain pertinent observations.

The fact that over 60 per cent of the patients were finally operated on or died of the disease is an expression of the inadequacy of nonoperative therapy during the early part of the period under study. Methods of nonoperative therapy have improved since then to the point where they have actually made the major contribution to a lower mortality, both operative and nonoperative. This is evidenced by the smaller number of patients (66.3 per cent) operated on under less than ideal circumstances in the years 1943-1949 as opposed to the period 1915-1942 (80 per cent). Furthermore, considering operations actually done during the two periods (as distinguished from the previously discussed group of patients first seen in 1915-1942, on whom some of the operations were done later than 1942), 72.9 per cent of the patients in the earlier and 44.2 per cent in the later period were operated on less than three years after onset — an expression of better control by nonoperative means. That no significantly fewer patients are receiving operative therapy in the later period as opposed to the former is testified to by the figures of 47 per cent of those admitted to the hospital who were operated on in the early and 44 per cent in the later years.

But during the later period the prevalence of carcinoma of the colon as a complication of ulcerative colitis has risen. The inescapable conclusion is that survival of more patients has produced more cancer without avoiding ileostomy.

What is needed is a means of predicting which patient will develop cancer. To date no real help in this respect can be given. The absence of pseudopolyposis in more than half the patients with cancer eliminates that finding as helpful. The absence of symptoms of increased activity of colitis, furthermore, has not prevented carcinoma from occurring. Thus, the only way to discover these frequently occurring carcinomas in patients with ulcerative colitis is by repeated x-ray and sigmoidoscopic examination.

Even patients with mild cases seem to be more prone to contract cancer than a normal person, as shown by the fact that cancer developed in patients with ulcerative colitis of long standing who were never sick enough to come into the hospital. Also, there were 4 cases of carcinoma in the colons of patients whose barium-enema examinations during the initial work-up showed only the most minimal signs of spasm or diminished haustral markings.

Of interest in our group is the presence of 2 patients who have survived after resection of the colon with cancer for over five years, and 2 more who have gone four years to date. This opposes the impression that cancer in ulcerative colitis is invariably incurable. But the youth of the patients, which leads to a higher grade of malignancy than is usually found in colonic carcinoma,[6] as well as the difficulty of recognition of symptoms, has made it a particularly unfavorable group.

We have not seen true ulcerative colitis develop proximal to an ileostomy. The disease, therefore, can be termed curable. In other words, if the handicap of ileostomy were not associated with the operation and the mortality were as low as early surgery should make it, it would be applied to all patients with the established disease. This balancing of handicap against risk of mortality creates a trying decision. On the basis of this survey, however, our position regarding indications for operative treatment is as follows: a period of two or three years of nonoperative management will accomplish something in the preparation of the patient for ileostomy even if the physicians in charge have little expectation that he will avoid eventual operative treatment; at the end of that period it will have been determined whether the patient is in the rare group in which the colonic changes as seen by proctoscopy and barium-enema study are partially or wholly reversible[7] (if they are not, even though he is asymptomatic, the patient should be advised that colectomy and ileostomy offer the safest course).

Such a program requires a degree of "salesmanship" on the part of the internist. The salesmanship has, in recent years, been made easier for him by the existence of organized groups of individuals with ileostomies[4,5] who help with advice to patients having trouble adjusting themselves to the concept of the handicap.

If the patient, having been apprised of these considerations, wishes to defer surgery, follow-up examinations with sigmoidoscopy and barium enema should be performed every six months as long as he retains his colon. Vigilance is as important in this respect as in that of gastric ulcer or adenomatous polyps of the colon.

The finding of 26 cases of small-bowel obstruction after colectomy or ileostomy seems formidable. Important lessons have been learned that we believe will lower the frequency of this complication and the mortality from it. At the time of colectomy great care is taken to reperitonealize all rough surfaces and to close the gutter lateral to the ileostomy. This is done with a continuous cotton suture, the anterior, lateral and posterior peritoneum, together with the mesentery of the ileum, being used. No such closure of the lateral gutter is done when ileostomy alone is performed, for the cecum fills in this area.

Once obstruction is diagnosed, immediate operation is indicated. It is important to remember that small amounts of ileostomy discharge do not rule out obstruction. It is of value to know that late obstruction is rare and that the patient can be assured

that, though complications do occur, eventual freedom from them is to be expected.

Summary and Conclusions

A follow-up study of 483 patients with ulcerative colitis seen at the Massachusetts General Hospital before 1943 is reported. Three hundred and forty-three were followed for ten or more years or to death. Two hundred and thirty-two patients (48 per cent) were eventually operated on for ulcerative colitis.

Over half the patients who were operated on or died without operation did so within the first three years. Most patients living aften ten years were under control whether treated with operation or without.

Carcinoma of the colon developed in 31 patients, 24 of whom are dead and 7 alive, 2 for more than five years, after operation.

Intestinal obstruction is an appreciable hazard after surgery for ulcerative colitis, but usually occurs within a year of the operation.

Improved nonoperative therapy has prolonged the time between onset of the disease and surgery and has made operation safer when it is necessary.

With the increased survival of patients with colons involved in ulcerative colitis, more cases of carcinoma are being discovered.

In any patient with a definite diagnosis of established chronic ulcerative colitis at the end of three years of treatment, colectomy and ileostomy should be recommended.

Patients who prefer the risk of cancer to the handicap of ileostomy should receive barium-enema and sigmoidoscopic study twice a year as long as the colon remains and regardless of symptoms.

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HORMONE EXCRETION BEFORE AND AFTER CASTRATION AND ADRENALECTOMY*

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BOSTON

FOURTEEN years have passed since Huggins and Hodges[1] demonstrated the efficacy of castration and estrogen therapy in the treatment of carcinoma of the prostate. The frequently observed response of this malignant process to hormonal therapy remains the most striking and promising phenomenon yet discovered in the study of cancer. However, the exact biologic mechanisms whereby retrogression of the neoplastic cell is brought about have not been elucidated. Further studies of the metabolic processes resulting from changes in hormonal environment will help define these mechanisms. In the first place it is indicated to measure the hormonal changes that occur during the course of such treatment. It is the purpose of this paper to present data obtained by both chemical and biologic study of hormones excreted in the urine of patients with carcinoma of the prostate before and during treatment. It is recognized that previous chemical studies of steroids of a similar nature from other laboratories have been reported,[2-6] but they have lacked the simultaneous biologic studies presented herewith.

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Method

The subjects in this group were all studied at the Peter Bent Brigham Hospital at some time during the last five years. All had tissue diagnoses of carcinoma of the prostate. Their age range at the time of diagnosis was fifty-two to eighty-two years. Determinations were performed on aliquots of twenty-four-hour urine specimens collected on ice. The following methods were used: biologic androgen assay by means of the comb-weight response of the immature chick[7]; follicle-stimulating-hormone assay with the use of the uterine weight response of the mouse[8]; and colorimetric measurement of 17-ketosteroids.[9,10] The animal-assay studies have been completed in 4 patients and are being done in an additional 7; 17-ketosteroids were measured before and after castration in 16 patients, who form the nucleus of the group.

Results

Biologic assay of urinary androgens in 4 men before and after castration revealed that in every case there

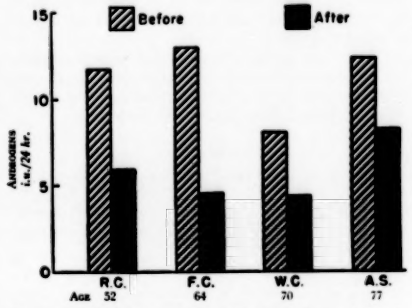

Figure 1. *Biologic Assay of Androgens Excreted in the Urine in Twenty-Four Hours before and after Castration in Patients with Carcinoma of the Prostate.*

A quantitative decrease in androgens excreted is found in each case after castration. It is noted that the smallest reduction occurred in the oldest patient of the group.

was a definite decrease in androgen excretion after castration (Fig. 1). All 4 men had low control values consistent with their ages. The range of 8 to 13 international units a day exhibited was in contrast to the higher range of healthy young men.[11] The postcastration values, recorded two days to five months after operation, ranged from 4 to 8 international units a day. In 3 of the 4 cases the decrease was 50 per cent or more. With the testes removed the adrenal cortex is assumed to be the source of the remaining androgens. In a general sense the decrease in total excretion of androgens observed may reflect the decrease in testicular androgen production in these elderly men.

In an attempt to demonstrate further the role of the adrenal cortex as a producer of androgen precursors, 25 units of ACTH was given intravenously to 5 castrated men and its equivalent in HP ACTHAR Gel* to a sixth. All showed an unequivocal rise in androgen excretion from an average of 6.5 to 15.1 international units a day. An elevation of at least 100 per cent occurred in every case (Fig. 2).

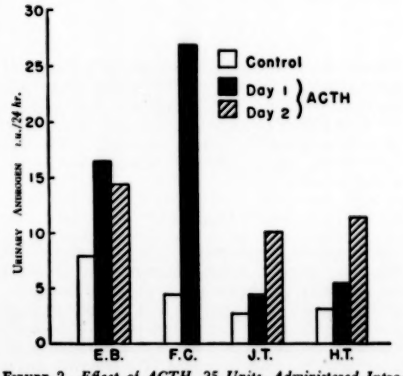

Figure 2. *Effect of ACTH, 25 Units, Administered Intravenously to 4 Castrated Men, Showing an Increase of More than 100 Per Cent in Biologic Androgens Excreted in the Urine in Twenty-Four Hours.*

The greatest response is seen in F.C., aged sixty-four years, and the least in the oldest patient, J.T., aged seventy-seven years.

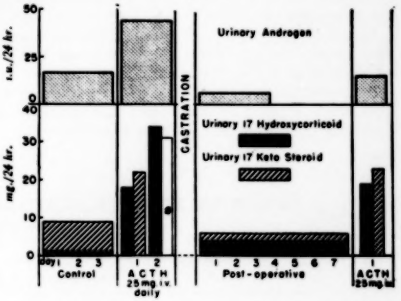

Figure 3. *Increased Excretion of Androgens in the Urine As a Result of ACTH (25 Units Intravenously) both before and after Castration in a Fifty-Two-Year-Old Man with Inoperable Carcinoma of the Prostate.*

An accompanying increase of both 17-hydroxycorticoids and 17-ketosteroids is shown simultaneously in response to ACTH both before and after orchiectomy.

One patient received ACTH intravenously both before and after castration. The control urinary androgen excretion was 11.6 international units a day. Two successive days of ACTH resulted in an average level of 53 units. The postcastration excretion of 5.9 units increased to 15.2 international units a day as a result of a single infusion of 25 units of ACTH (Fig. 3).

The data presented in Figure 1 are of interest in the study of the mechanism of response of carcinoma of the prostate to treatment by orchiectomy. A measured reduction of androgens is shown that is sufficient to bring about significant alteration in the metabolism of biologically susceptible cells such as those of prostatic carcinoma. In a similar manner the data in Figure 2 are of interest in the study of the possible mechanisms involved in the reactivation of carcinoma of the prostate that usually occurs after an antecedent response to orchiectomy. Androgen excretion present

*Kindly supplied by Dr. Richard A. Carey, Armour Laboratories, Chicago, Illinois.

after orchiectomy has been shown[12] to be largely from the adrenal cortex. The potential of increased androgen secretion by the adrenal cortex in response to a physiologic stimulus is presented graphically in Figure 2 in castrated men and in Figure 3, in which the response to ACTH is seen both before and after orchiectomy to result in an increased excretion of androgen in the urine. The question, therefore, is, Does the adrenal cortex in daily life respond to stress and stimuli from the pituitary in castrated men by an intermittent increased production of androgens, and is this an important factor in the reactivation of carcinoma of the prostate? It seems reasonable to assume that 25 units of ACTH does represent an analogy to normal physiologic pituitary stimuli and that the resulting increased androgen production is of metabolic significance. These findings furnish further indications for investigation of the effect of adrenocortical inhibition and of total adrenalectomy on carcinoma of the prostate.

In the evaluation of data obtained by study of castrated men subjected to a total adrenalectomy for advanced prostatic cancer, several factors must be considered. In the first place the patients in the present study who had this procedure were truly in a terminal stage. Secondly, they required maintenance doses of hydroxycorticoids that may themselves be androgenic precursors.

In all 4 patients in whom biologic androgens were measured before and after adrenalectomy the preoperative level was low for even an elderly castrated man. Yet adrenalectomy resulted in attainment of a still lower level — less than 2 international units a day (Fig. 4). Withdrawal of cortisone for as long as five days did not further lower this level. Androgenic activity was still present in the urine at the end of this period. Although administration of increasingly larger doses of cortisone and hydrocortisone resulted in increases in androgen excretion,[13] it has been concluded that maintenance doses (25 to 50 mg. a day) may be administered to adrenalectomized castrated men without an appreciable rise in urinary androgen excretion.

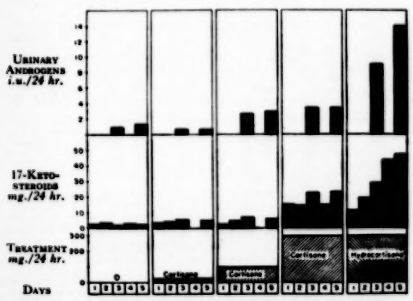

FIGURE 4. *Urinary Androgen and 17-Ketosteroid Excretion in a Fifty-Four-Year-Old Man with Carcinoma of the Prostate after Orchiectomy and Adrenalectomy (Reproduced from Harrison et al.[11] with the Permission of the Publishers). It is noted that 0.06 to 1.0 international unit of androgen was present in the urine of a castrated, adrenalectomized man even when cortisone acetate was stopped for five days. At the same time very slight traces of 17-ketosteroids were found in the urine. It is noted that an increase in the dose of cortisone acetate raised 17-ketosteroid and androgen excretion. Similar doses of hydrocortisone caused a much greater increase of each in the urine.*

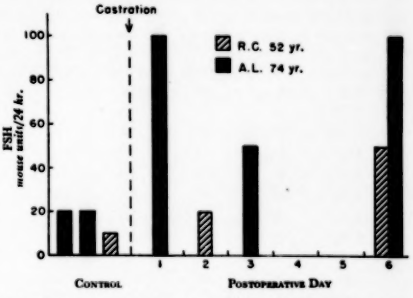

FIGURE 5. *Immediate Rise of Pituitary FSH in the Urine after Castration of 2 Men in the Sixth and Eighth Decades. In R.C. the rise was maximal in twenty-four hours, and the other showed a continued increase during the ensuing week.*

It seemed desirable to determine if there is any immediate and subsequent measurable effect of castration on the pituitary glands of the patients with carcinoma of the prostate. Since these studies were begun, assays of follicle-stimulating hormone (FSH) have become available to this laboratory. A high FSH excretion — more than 50 mouse units a day — has been noted by several observers in male patients some years after castration. This phenomenon has been compared to the similar levels found in menopausal and castrated women, release of the anterior pituitary gland from gonadal inhibition being cited as the mechanism.

In the present study a total of 11 determinations were made in 5 castrated men. Only 1 subject failed to show a level of at least 100 mouse units a day — a marked increase over the level usually found in intact men. Two men had FSH determinations before and shortly after castration (Fig. 5). Both showed precastration levels of less than 50 mouse units a day. After castration both showed a rise within five days to a level of at least 50 mouse units a day.

One castrated man was studied before and after adrenalectomy; on each occasion he excreted between 100 and 200 mouse units a day. Estrogen therapy with TACE, 12 to 24 mg. a day, did not appear to affect FSH level in the 3 castrated men in whom that measurement was carried out.

Discussion

The effect of castration on the urinary 17-ketosteroid excretion of these elderly patients is not always consistent. The 16 men studied varied in their responses. Levels were recorded before and at multiple intervals from two to twenty-one days after castration. All but 2 showed a decrease of average values after castration; the over-all means were 7.4 mg. a day before and 5.2 mg. a day after castration. However, only 4 of the 16 showed an average decrease of more than 3 mg. a day. It is open to question whether changes below this decrement are significant. The prevailing low level of 17-ketosteroid excretion in the age group of these patients makes it difficult to demonstrate a significant decrease (Table 1).

Table 1. *17-Ketosteroid Excretion in Men with Prostatic Cancer before and during the First Three Weeks after Castration.*

Patient	Age	17-Ketosteroids		
		Before castration	After castration	Mean change
	yr.	mg./day	mg./day	mg./day
R.C.	52	8.8	6.1	−2.7
W.F.	59	8.0	5.4	−2.6
E.B.	64	8.0	5.7	−2.3
F.C.	64	6.4	5.9	−0.5
B.M.	65	5.8	4.0	−1.8
W.C.	70	7.1	6.6	−0.5
A.P.	70	5.4	5.3	−0.1
S.W.	70	11.7	7.1	−4.4
H.A.	72	6.4	2.5	−3.9
R.S.	73	8.8	6.5	−2.3
A.L.	74	5.0	5.2	+0.2
A.S.	77	6.1	7.9	+1.8
W.J.	78	6.8	3.3	−3.5
W.N.	79	5.5	5.2	−0.3
F.B.	80	12.9	3.6	−9.3
C.M.	82	6.0	3.4	−2.6
Averages		7.4	5.2	−2.0

The total urinary excretion of 17-ketosteroids affords at best a rough guide to the relative state of gonadal and adrenal function. Without fractionation studies it is unwarranted to draw final conclusions regarding androgen from studies of the total 17-ketosteroids alone. From these data it is inferred that castration did not greatly alter the 17-ketosteroid excretion in most of these elderly subjects. No appreciable difference in 17-ketosteroid excretion was noted between untreated and estrogen-treated patients before and after castration.

Summary and Conclusions

Castration of patients with carcinoma of the prostate caused a prompt decrease in excretion of biologic androgen, a prompt rise in excretion of follicle-stimulating hormone (FSH) and a small decrease or no appreciable change in 17-ketosteroids.

ACTH caused an increase in biologic androgen excretion of 100 per cent or more in both intact and castrated men with prostatic cancer. This indicates that an intact pituitary-adrenal system is a potential source of stimulus to the reactivation of prostatic carcinoma.

Total adrenalectomy in castrated men caused significant diminution of biologic androgens but, even when hydroxycorticoid therapy was interrupted, did not eliminate them completely.

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SURGICAL TREATMENT OF LUNG CANCER FOUND ON X-RAY SURVEY

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ASYMPTOMATIC lung cancer, discoverable only by x-ray examination, has a higher rate of resectability and a greater potential curability than symptomatic cancer. Pessimism should not deter the search for silent cancer in mass chest surveys and individual chest screening. An effective use of x-ray examination by the medical profession combined with the intelligent co-operation of the public will uncover more lung cancers at the most favorable time for cure.

EXPERIENCE

In support of this contention, we present the experience of the Overholt Thoracic Clinic with 46 cases of silent lung cancer seen between December, 1947, and August, 1953. (This represents 4.2 per cent of our total experience with 1100 histologically verified cases of lung cancer.) All were discovered by x-ray survey of the chest before the onset of any symptoms. Every case of histologically proved survey-discovered lung cancer is reported. Unfortunately, however, not all these patients arrived promptly for consultation, and in 18 (39 per cent) symptoms attributable to the lesion developed. The median delay was six months. Even so, the salvage at that time appears remarkably higher than that in patients who were symptomatic at the time of first x-ray examination.

Thirty patients of the survey group were first seen three or more years ago, between December, 1947, and April, 1951 (Table 1). In 24 (80 per cent) a histologic diagnosis could not be made until the chest was explored. Twenty-six (87 per cent) were explored; the exploration rate in 263 symptomatic cancers for the same period was appreciably less, 64 per cent. Twenty-three (77 per cent) were resected; the resection rate in symptomatic cancers for the same period was only 38 per cent. In 13 (57 per cent) of the 23 resected specimens microscopical examination revealed no extension to lymph nodes, and there were no known metastases; this group is recorded as "favorable" in Figure 1. In the simultaneous experience with symptomatic lesions 40 per cent of the resected specimens showed no extension beyond the lung.

TABLE 1. *Data in Survey-Detected and Symptomatic Cancers of the Lung.*

GROUP	NO. OF CASES	EXPLORATIONS	RESECTIONS	FAVORABLE CASES*	3-YR. SURVIVALS
Cancer detected by survey	30	26(87%)	23(77%)	13(43%)	9(30%)
Symptomatic cancer	263	168(64%)	100(38%)	40(15%)	32(12%)

*No extension to lymph nodes & no metastases.

Of the 30 patients with lung cancer found by survey and seen over three years ago, 9 are alive and well, without evidence of recurrence. This result represents a three-year-survival rate of 30 per cent as compared with one of 12 per cent for the symptomatic group. Five of the 9 patients surviving were treated within six weeks of the x-ray survey; 1 was treated four months after x-ray study. The remaining 3, although not treated as promptly, are classed as having bronchiolar adenocarcinoma (papillary adenocarcinoma, mucinous adenocarcinoma and alveolar carcinoma), a slowly growing, favorable type of tumor.[1] Although this survey group includes only 30 cases, its statistics are consistently so much better than those of the symptomatic group that we are unwilling to discount the principle of finding early lung cancer by x-ray survey. Instead, we urge that continued use be made of x-ray surveys and that individual x-ray screening be more generally encouraged.

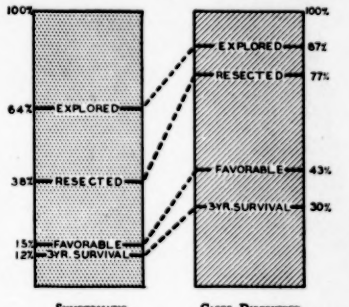

FIGURE 1. *Resectability and Three-Year Survival in 263 Symptomatic Cancers and in 30 Discovered on X-Ray Survey.*

The 16 patients remaining from the total survey group of 46 were seen for the first time within three years. Ten are living more than a year since resection.

DETECTION

To discover abnormal shadows in the lung all available means of chest screening should be utilized.

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Suspicious shadows, whether found during mass tuberculosis surveys or on x-ray films taken by individual doctor-patient arrangement, will represent earlier disease more amenable to cure if periodic x-ray examination is done at reasonably short intervals. In view of recent publications[2,3] it might be wise to give particular attention to male patients over the age of forty years, especially those who have been avid smokers. Fortunately, x-ray screening of the chest has become more frequent in medical and business practices. Mass x-ray surveys for tuberculosis have increased the awareness of both medical and lay public to the value of periodic examination. Factories, schools, union clinics, fraternal and social organizations, hospitals, governmental agencies and many others already conduct such screenings. Gradually, more adequate programs are being devised to follow the diagnostic course of every patient with an abnormal x-ray shadow.

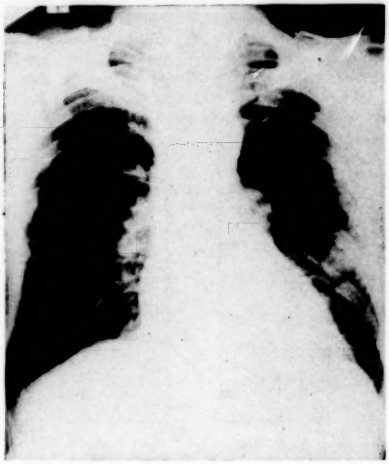

FIGURE 2. *Roentgenogram of the Chest in A.B., a Fifty-Eight-Year-Old Man.*

At the time of x-ray survey by a mobile unit the patient was without symptoms. Although informed of his pulmonary abnormality, he delayed for five months until cough and expectoration prompted him to visit his physician. Two weeks later pneumonectomy on the left was performed for epidermoid carcinoma, Grade 2. There was no evidence of recurrence four years later.

Typical cases in our experience are shown in Figures 2 to 5.

More practicing physicians and life-insurance companies would do well to adopt x-ray study of the chest as part of the routine and periodic health examination of their patients and clients. The individual physician should accept the responsibility of arranging periodic x-ray examinations for his patient. All available x-ray technicians and apparatus could be utilized. The minimum examination of the lung fields should include a single posteroanterior film, either miniature or full size. In the interests of economy and practicality, complete radiologic study, with special views, fluoroscopy and clinical examinations, in asymptomatic patients should be reserved for those with suspicious findings on the screening films.

SUSPICION

Physicians interpreting films must have a suspicious attitude, for lung cancer, even in this silent phase, frequently masquerades as tuberculoma, fibroid tuberculosis, pneumonia or bronchiectasis. The very presence of a lung lesion without lung symptoms should arouse suspicion of cancer. We cannot agree with investigators who state that x-ray changes do not precede symptoms in lung cancer.[4] Here is a review of 46 cases in point. Between December, 1947, and August, 1953, at the Overholt Thoracic Clinic exploration was carried out on 268 patients who had abnormal pulmonary shadows on x-ray survey and who were asymptomatic at the time of the survey. Of these, 18 per cent (46) proved to have primary

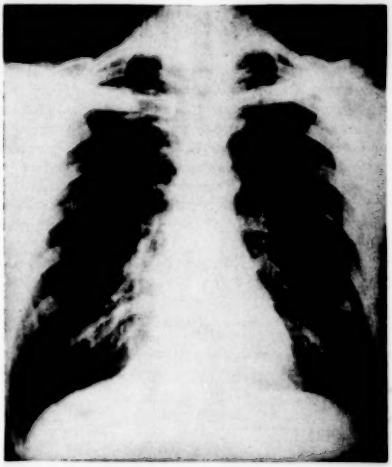

FIGURE 3. *Roentgenogram of L.L., a Forty-Three-Year-Old Man with a Peripheral Tuberculoma.*

Thoracotomy, wedge excision and histologic examination established the diagnosis. Total excision solved the problem two months after the results of x-ray survey were reported to the patient as showing a suspicious shadow in the left lung. Four years later he was well and working.

pulmonary carcinoma.* Harrington,[5] who operated on 16 patients with asymptomatic intrapulmonary lesions, found 1 malignant adenoma and 2 primary and 3 metastatic cancers. Grow, Bradford and Mahon[6] reported 19 per cent of 86 circumscribed, undiagnosed intrathoracic lesions to be malignant. Hood et al.[7] observed bronchogenic carcinoma in 16 per cent of 156 resected solitary circumscribed x-ray lesions of the lung.

The spherical "coin-shaped" lesion is the commonest x-ray appearance in the asymptomatic group. This means simply that the lesion has not extended to occlude a bronchus. Satellite nodules, smooth outline and lack of demonstrable change over a period of months, or even of years, do not rule out cancer. Diffuse calcification throughout an x-ray shadow, however, is usually a dependable criterion of a benign lesion. Serial x-ray examination of the chest to demonstrate possible change in the size of the shadow is most undependable, wastes time and may sacrifice a life. The phrase so frequently seen on the x-ray report, "advise repeat in one to three months," may be a harbinger of disaster — even occasionally in nonmalignant lesions.

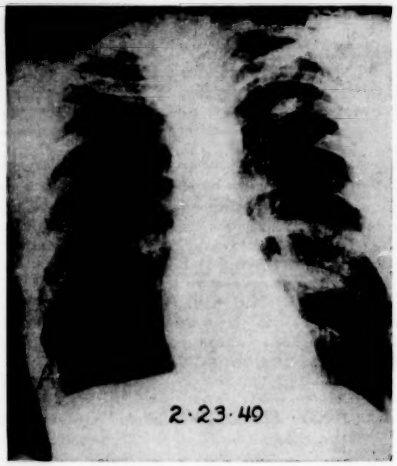

FIGURE 4. *Roentgenogram in H.G., a Fifty-Two-Year-Old Man.*

X-ray screening on application for employment disclosed an abnormal shadow in the left apex. Investigation consisted of a tuberculin skin test, which was reported negative. Action rested on the suggestion, "repeat x-ray in one year."

*Seventy-two of the 268 were considered cancer suspects after study failed to give a diagnosis. Surgical exploration of this group revealed tuberculoma (11), tuberculosis (6), hamartoma (9), bronchial adenoma (1), pericardial cyst (7), bronchogenic cyst (6), respiratory-epithelium cyst (4), dermoid cyst (2), fibrous-lined cyst (2), pleural cyst (1), benign thymic cyst (1), bronchiectasis (4), neurofibroma (1), chronic pneumonitis (4), nonspecific pleuritis (3), lipoid pneumonia (2), nonspecific granuloma (2), blastomycosis (1), histoplasmosis (1), amyloid (1), aneurysm of the pulmonary artery (1), diaphragmatic hernia (1) and chondroma (1). Cancer was excluded or considered unlikely as a preoperative diagnosis in 150 cases subsequently found to be tuberculosis (111), tuberculoma (15), bronchiectasis (6), pheochromocytoma (1), ganglioneuroma (5), neurofibroma (7), diaphragmatic hernia (6) and osteochondroma of rib (1).

DECISION

The key to a higher cure rate is efficiency in selecting and managing patients whose x-ray examinations, survey or not, reveal a lesion suggestive of tumor. When any suspicion of lung cancer is aroused, a direct approach to the diagnosis is clearly indicated. Thoracotomy is a valuable early diagnostic procedure when exact diagnosis cannot otherwise be made. The patient's comfort should not be disturbed, nor time and money wasted on extensive searches for possible primary sites of cancer unless symptoms or physical findings suggest such a site. The Papanicolaou test has been accurate in only 3 out of 4 verified lung cancers, even in the hands of the most experienced investigators. Used by inexperienced technicians, it is worthless as a guide. A negative cytologic test of sputum and bronchial secretions does not rule out the necessity of chest exploration, and a positive test demands exploration. A reasonable search for acid-fast bacilli may be justified when there is a real suspicion of tuberculosis. However, the usually silent "coin" lesion, whether granulomatous or neoplastic, is better removed. Delays of eight

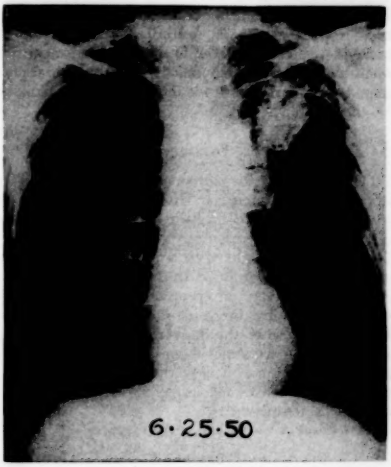

FIGURE 5. *Roentgenogram of Patient Shown in Figure 4. Sixteen months after the first abnormal x-ray film cough and hoarseness developed. X-ray study then showed an advance of the lung lesion. A paralyzed diaphragm and vocal cord precluded thoracotomy in the face of the x-ray evidence of mediastinal invasion by the tumor. The patient died two months after referral to the surgeon.*

weeks while sputum cultures or guinea-pig inoculations are awaited are not justified.

Bronchoscopy, like sputum study, is valuable for diagnosis only when positive and, in silent lesions, is rarely successful diagnostically. Its most helpful function is as a preliminary to contemplated thoracotomy to inspect the air passages for gross evidence of nonresectability. In our experience a patient suspected of having lung cancer is admitted to the hospital usually one or two days before operation. Unless clinical evaluation or x-ray study gives evidence that resectability is doubtful, bronchoscopy is performed under topical anesthesia immediately before exploration of the chest. Patients with lesions appearing advanced by x-ray or clinical study are bronchoscoped a day or two in advance of the date planned for thoracotomy.

Excision

The plan of surgical management proceeds from bronchoscopy to incision. Histologic diagnosis is the first concern. Tissue for this diagnosis may be obtained from enlarged lymph nodes or by resection of the lesion. In patients with small, superficial lesions a wedge resection may be safe. In larger or deeper lesions a segmental or even lobar resection is performed. Biopsy by direct incision into a lesion is less desirable because of the danger of implanting tumor cells. A frozen section is examined histologically. If the resected lesion is benign the thorax is closed. If it is malignant appropriate lobectomy or pneumonectomy is completed.

Conclusions

Asymptomatic lung cancers can be discovered by x-ray screening of the chest and are, in our experience, more often resectable, less extensive and more curable than symptomatic cancers.

More lung cancers found will be favorable for cure if men over forty are given x-ray examinations of the chest at least annually, and preferably semiannually if they are heavy cigarette smokers.

More survey-detected cancers will be cured if there is a continued education of the public concerning the value of x-ray screening, if efficient management makes as short as possible the interval from detection of shadow to therapy of lesion and if a bona fide x-ray shadow suspicious of cancer in the chest is considered sufficient evidence in itself to indicate early exploratory thoracotomy.

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MEDICAL PROGRESS

COAGULATION, HEMORRHAGE AND THROMBOSIS*

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"DAS Blut ist ein besonderer Saft" (Goethe).

During the past decade research in coagulation, one of the vital homeostatic functions, has been in a state of intense ferment. As a consequence, notable advances have been made, and substantial clarification has been achieved in this field, long known for its confusion and bitter controversy. Knowledge has come from many disciplines — human and comparative physiology, biochemistry, physical chemistry, animal husbandry, pathology, genetics and, not least, clinical investigation — reflecting the multifaceted background required of the student of this subject.

As has been aptly pointed out,[1] the ordinary physician is no longer justified in regarding the subject with tolerant detachment. The patient with abnormal coagulation and disordered hemostasis can now benefit enormously by a far more rational approach to his disease than was hitherto possible. Moreover, the pathogenesis and management of thromboembolic disease is being subjected to direct experimental study with considerable promise of success. The future appears bright indeed.

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It would be folly to attempt here a complete review of all recent progress. This report is restricted to a description of some of the notable advances, a consideration of certain topics under active exploration and the indication of gaps in knowledge in urgent need of investigation. The hemorrhagic disorders are reclassified in the light of present knowledge, and the diagnostic and therapeutic approach to a "bleeder" is discussed. In addition thrombotic disease, as the other side of the coagulation coin, is briefly reviewed. Throughout, an effort is made to demarcate fact from fancy, a distinction far too infrequently made in this entire field.

For those seeking more detailed information certain more exhaustive treatises are suggested.[1-4] The reader may also find exceedingly useful recent periodic reviews[5-8] and compilations of literature.[9]

Although it is generally recognized that normal vascular function, particularly of the small vessels, plays an important part in hemostasis,[10-12] there is far less understanding of this area than of the clotting mechanism itself. This is unfortunate because in approximately 50 per cent of all cases of hemorrhagic diathesis, no abnormality in coagulation is demonstrable despite the newer knowledge.

There can be little question, also, concerning the connection between vascular abnormality and the clotting disturbance associated with thrombocytopenic purpura; the platelets appear to be the keystone connecting the vascular tree with the clotting mechanism.[10,12] Moreover, as shown below, abnormalities in both vascular and coagulation factors may have significant pathogenetic roles in certain other hemorrhagic syndromes. Because of inadequate knowledge, however, and more particularly because coagulation per se is intended to be the major subject under review, vascular factors concerned with hemostasis receive little further consideration.

The classic scheme of coagulation, now recognized as completely inadequate to explain existing knowledge, will nevertheless be found useful as a guide:

$$\text{Platelet} + \text{"Foreign Surface"} \longrightarrow \text{Thromboplastin}$$

$$\text{Thromboplastin} + \text{Prothrombin} \xrightarrow{Ca++} \text{Thrombin}$$

$$\text{Thrombin} + \text{Fibrinogen} \longrightarrow \text{Fibrin.}$$

To this skeletal outline, comprising three major sequential steps, have been added other processes (Fig. 1) essential to a mechanism superbly designed to permit, when needed, the ready, smooth and rapid mobilization of a series of beautifully integrated and unimaginably complicated reactions involving surface phenomena, electrostatic forces, interaction of cells with proteins, of proteins with proteins* and of proteins with metals. Under normal circumstances, particularly when hemostasis is not threatened, this involved mechanism either is held in complete abeyance within vascular channels or at most proceeds extremely slowly.

Still basic are the three major steps, which are maintained for convenience in the more complicated modern scheme. The reader, however, is strongly encouraged to avoid the static implication of the chart, and rather to think in terms of a dynamic process that, dormant and yet delicately poised in the circulating blood, is triggered, then assuming ever increasing velocity, wherever a break in vascular integrity occurs, until the final goal of hemostasis is achieved. The importance of emphasizing *dynamics* rather than quantity is clearly illustrated by the fact that in many hemorrhagic disorders, large and voluminous clots may form but simply not fast enough.

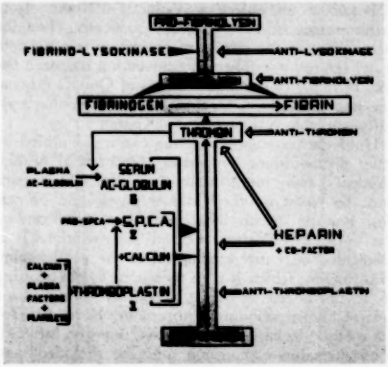

FIGURE 1. *Modern Scheme of Coagulation.*

METHODS

"If arithmetic, mensuration and weighing be taken from any art that which remains will not be much" (Plato).

In coagulation, as in many other scientific areas, substantial advance has followed notable contributions in methods of mensuration. Detailed delineation of general considerations, objectives, principles and procedure of many of these methods will soon be available.[13]

Prothrombin

It is fair to state that the Quick one-stage prothrombin method[14] provided an extremely valuable clinical laboratory test, as well as a tremendous stimulus for progress in coagulation research. It consists of measuring the plasma clotting time (prothrombin time) after the addition of optimal amounts of throm-

*It is of interest that coagulation is one of the few biologic phenomena in which protein-protein interaction has been demonstrated to have both physiologic and pathologic significance. In this connection one may also cite immunologic and proteolytic systems. It is perhaps significant that many of the phenomena in these areas are strikingly similar, if not more closely related, to those observed in blood clotting (the fibrinolytic mechanism, the relation of prothrombin to components of complement and so forth).

boplastin and calcium. This time is the minimal interval that elapses before a macroscopic fibrin clot results from the conversion of prothrombin to thrombin. In the light of present knowledge it reflects, among other things, the velocity and amount of thrombin formation from the interaction of prothrombin with calcium, thromboplastin and certain "accessory" substances; the velocity of the thrombin-fibrinogen interaction and deposition of the insoluble fibrin gel; and the competitive effect of antithrombin inactivating the thrombin. Obviously, the prothrombin time may not be a measure of prothrombin alone unless the other variables are adequately controlled.[12,15] Although the one-stage method cannot therefore be considered specific for prothrombin, its enormous clinical usefulness needs no elaboration. It should be remembered, however, that the purpose of the test is to measure the over-all velocity of thrombin elaboration, an objective distinctly different from measurement of prothrombin specifically. For the latter purpose the one-stage procedure is subject to many limitations. Their circumvention has been the goal of many of the modifications of Quick's original one-stage procedure. Of these, the most reliable presently available is the method of Owren.[13,16]

Until the coagulation factors can be identified by other distinguishing properties (biochemical or biophysical), assay methods for these "trace"* proteins must be based on their known physiologic properties. For the specific determination of prothrombin, the so-called two-stage method[17] is essential. It is predicated on entire conversion of the prothrombin to thrombin, which is then measured by the clotting of a fibrinogen solution previously standardized against known amounts of thrombin. Here, also, for the method to be valid, all factors required for complete thrombin elaboration must be provided, and thrombin inactivation (by antithrombins) must be avoided or minimized. For routine purposes the original procedure is satisfactory, but in my experience supplements of serum prothrombin conversion accelerator, essential for complete prothrombin conversion, must be provided whenever deficiency of this substance exists pathologically in the plasma or when accelerator-poor prothrombin fractions derived from plasma are assayed.

Antihemophilic Factor

Recent methods for the determination of other factors deserve brief mention: antihemophilic factor can now be measured by its corrective effect on the clotting defect (the poor prothrombin conversion) of hemophilic blood[18,19] (Fig. 2 and 3). This procedure is admittedly involved and laborious, and has the additional disadvantage of requiring that freshly shed hemophilic blood be available whenever the test is performed. In specificity and accuracy, it is far superior to older procedures based upon shortening the elevated clotting or recalcification times of hemophilic blood. It is now recognized that substances besides antihemophilic factor may do this and yet be unable to rectify the poor prothrombin consumption.

*Except for fibrinogen most of the factors exist in plasma in "trace" amounts. Available evidence indicates that prothrombin, serum prothrombin conversion accelerator, accelerator globulin and probably antihemophilic factor each comprise considerably less than 20 mg. per 100 cc. of plasma.

Plasma Thromboplastic Component

This recently disclosed clotting factor can be similarly assayed, in this instance by its effect on the poor prothrombin consumption of blood from patients known to be deficient in the component. This method also requires fresh blood from patients with this uncommon disease, virtually limiting the procedure to research laboratories.

Thromboplastin Generation Test

Brief mention should be made of this procedure, which, as applied to components essential to the elaboration of thromboplastic activity, promises to become clinically important in distinguishing disorders due to disturbed clotting in its early phase[1,20] (these disorders are discussed at length in the second section of this review). Present knowledge indicates that thromboplastic activity arises from the interaction, in a manner as yet completely unknown, of platelets, antihemophilic factor, plasma thromboplastic component and perhaps other plasma constituents. Obviously, deficiency in any one, or combination, of these entities will result in inadequate or retarded thromboplastin formation. By providing optimal amounts of all but one of these factors, a test system is made available that will be critical for the entity in question. The procedure can thus disclose qualitative platelet abnormalities, derangements in antihemophilic factor and thromboplastic component and other clotting anomalies associated with disturbed thromboplastin formation.

Prothrombin Consumption Test

The diagnostic value of this test has now been established beyond question. The physician is therefore justified in requesting it of routine clinical laboratories. Its underlying principle is exceedingly simple: when normal blood is placed in a glass test tube, most of the prothrombin will disappear (presumably in its conversion to thrombin) within sixty minutes after the blood is shed. Under certain pathologic conditions — hemophilia, deficiency of plasma thromboplastic component, "hemophilioid" disease and circulating anticoagulants, occasionally pseudohemophilia, thrombasthenia, thrombocytopenia, accelerator-globulin deficiency, severe deficiency of serum prothrombin conversion accelerator and probably other hemorrhagic states — the residual serum prothrombin is far greater after coagulation is allowed to run its course than under normal circumstances. Accordingly, serum containing less than 15 per cent of the parent plasma prothrombin may be considered strong evidence against any of these coagulation defects. Thus,

the test, involving simply the determination of plasma and serum prothrombin,[21-23] is extremely useful as a diagnostic screening procedure, whereby a normal value readily excludes many serious hemorrhagic disorders. Its usefulness is clearly apparent in obscure bleeding in infants when venous blood is not easily obtained; several drops of blood from a freely bleeding heel stab can provide sufficient serum for determining the prothrombin consumption, not to mention other important tests. Under these circumstances a high* residual serum prothrombin is extremely informative.

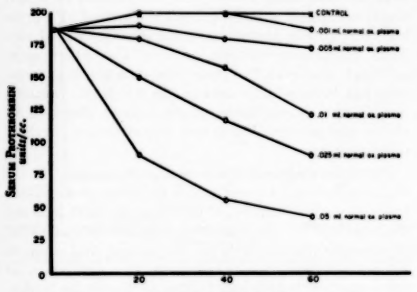

FIGURE 2. *Effect of Normal Human Plasma on the Prothrombin Consumption of Clotting Hemophilic Blood (Reproduced from Alexander" with the Permission of the Publishers).*

The hemophilic blood was drawn with an Arquad-coated needle and silicone-coated syringe. The first several cubic centimeters were discarded, and a fresh syringe was attached to the needle lying within the vein; 2 cc. of blood was placed in ordinary glass clotting-time tubes containing the amounts of normal plasma indicated. The tubes were promptly inverted once to assure adequate mixing, and at specified intervals 0.15-molar sodium oxalate was added (1.0 vol. to 9 vol. of blood) to stop the coagulation process. The "serum" was then analyzed for prothrombin by the modified two-stage method in which optimal amounts of accelerator globulin are provided by bovine barium carbonate adsorbed serum."

Accelerator Globulin

A relatively simple method is now available for measuring accelerator globulin. Because the substance is essential for the physiologic† conversion of prothrombin to thrombin by thromboplastin and calcium and because it is a labile protein whose activity disappears from aging plasma, it is assayed by its ability to correct the retarded prothrombin conversion (elevated prothrombin time) of stored oxalated human plasma.[24,25] Values are most conveniently expressed in terms of normal pooled plasma tested concurrently. The two-stage procedure, using purified prothrombin, is also employed for measuring accelerator globulin.[26]

Serum Prothrombin Conversion Accelerator System

Reliable methods are now available for assaying this factor, which is also essential for physiologic prothrombin conversion.[13,27,28] Since, in its absence, prothrombin conversion is negligible despite the presence of optimal amounts of all other known essential clotting constituents, the conversion accelerator is best measured by its effect in lowering the elevated prothrombin time of a system originally, or artificially rendered, deficient in this moiety. Such a system is best provided by blood from subjects with marked accelerator deficiency (only a handful of such patients are presently known) or by bovine plasma from

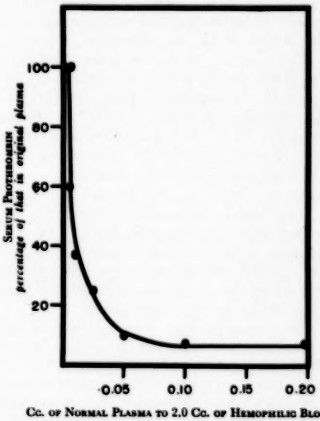

FIGURE 3. *Relation between AHF Concentration and One-Hour Prothrombin Consumption.*

Two-stage" prothrombin values in hemophilic serum were obtained an hour after hemophilic blood mixed with normal oxalated plasma. Hemophilic blood contained 48 per cent packed cells, and may be assumed to have contained 0 AHF.

which the accelerator system has been removed by adsorption. For technical and other reasons these procedures are not ready for adoption by laboratories performing routine assays.

Other advances in methodology that should be mentioned are as follows: tests for hypocoagulability and hypercoagulability with heparin-protamine titration procedures[29]; determination of heparin or heparinlike substances[30,31]; tests for platelet agglutinins

*A normal value is less significant since without unclotted blood there is no way of knowing what the *plasma* prothrombin was. Thus, hypoprothrombinemia may be undetected.

†In contrast to "nonphysiologic" prothrombin conversion, as with concentrated citrate and other electrolytes, which is discussed in the second section of this review.

in thrombocytopenic purpura[32,33]; measurement of antithrombic activity[34]; and assay of fibrinolysin activity.[35]

First Phase of Coagulation: Elaboration of Thromboplastic Activity

"A series of judgments, revised without ceasing goes to make up the incontestable progress of science" (Duclaux).

Fluidity of Blood and Initiation of Clotting Sequence

What initiates the clotting sequence when blood is shed? What makes the reaction "take off"? This cardinal question, of considerable practical as well as academic importance, remains unanswered despite many advances in knowledge. Pertinent, also, is the question of what maintains the fluidity of the blood within vascular channels where apparently all the ingredients essential for clotting are present. The conclusion seems inescapable that some substance, or condition essential for clotting, is lacking, or that an anticoagulant is present. Despite painstaking search, there is still no evidence that circulating heparin keeps the blood fluid, as originally proposed by Howell. The amount of this anticoagulant demonstrable in blood under normal circumstances is far too little to be responsible.[31] Even under obscure pathologic conditions in which heparin* or "heparinoid" substances have been suspected as explaining an obvious clotting disturbance, supporting (to say nothing of convincing) evidence is lacking.

According to Tocantins and Carroll,[38] circulating blood is kept fluid by an antithromboplastin, which they have separated and partially purified by extraction of plasma. Determination of whether the product is the "natural anticoagulant" or arises partly as a consequence of the procedure to which the plasma is subjected awaits further investigation.

It may be postulated that coagulation does indeed proceed continuously within the circulation, although extremely slowly as compared with shed blood. Consistent with this concept are observations regarding the rate at which certain clotting factors, some known to be consumed during in vitro coagulation, disappear from the circulation after administration in clinical states characterized by their respective deficiencies. Thus, in hemophilia, infused antihemophilic factor virtually disappears within twenty-four hours[39]; in primary or secondary thrombocytopenic purpura most of the infused platelets disappear within two or three days[40,41]; in parahemophilia, administered accelerator globulin is practically gone after forty-eight to seventy-two hours[42,43]; in deficiency of serum prothrombin conversion accelerator, supplements disappear within less than twenty-four hours[44]; and in congenital afibrinogenemia the half life of administered fibrinogen is about twenty-four hours.[45] Since many of these substances show far greater stability in vitro, it is reasonable to assume that their disappearance in vivo reflects a slow but steady consumption within the body in connection with their clotting function. The same changes occur in shed blood (without added anticoagulant) but much more rapidly. Also compatible with the concept advanced above is the demonstration of preformed thrombin (bound by antithrombin, and thus inactive) in the blood.[46]†

Surface Phenomena

It has long been known that the surface to which blood is exposed greatly influences clotting. Progress has been greatly furthered by the introduction of surfaces comprising silicone, plastics and other nonwetting‡ materials.[47] Their clot-decelerating property has been widely used in the clinic, in research and in the development of procedures designed to obtain and preserve blood and its constituents in their natural state.

Precisely which clotting factor (or factors) is directly influenced by surfaces is far from clear. Contrary to earlier opinion, it now appears that it is not the platelets.[48,49] Fragmentary evidence indicates that electrostatic forces, vis-à-vis the surface and some as yet unidentified plasma proteins, are significant in this regard.[50,51] The implication of this in the pathogenesis of thromboembolic disease has long been suspected, but existing knowledge in this regard is hopelessly inadequate.

Platelets

Basic aspects. Of the recent advances, those relating to the platelets have been among the most outstanding. Despite general agreement concerning their importance in the elaboration of thromboplastic activity,§ debate continues regarding whether *complete* removal of platelets would induce *complete* incoagulability, a question of only theoretic interest at present. It is well established, however, that thrombocytopenia, spontaneous or induced, results in retarded and incomplete coagulation, reflected in retarded or incomplete prothrombin conversion.[21] This defect, clearly evident in Figure 4, is readily rectified both in vitro and vivo by restoration of the platelets to normal. A similar defect is demonstrable in so-called thrombas-

*To my knowledge only 1 case has been described[36] in which the evidence was more than suggestive that the disturbance in coagulation was due to spontaneously arising excesses of circulating heparin. It comes as a surprise to learn, moreover, that although heparin has been prepared from many animal species, *human* heparin has never been obtained despite many attempts by outstanding investigators.[37]

†This has not as yet been confirmed.

‡Wettability and nonwettability are thought to define the conditions that favor or prevent the clotting process. Although this correlation may be generally true, a notable exception is the fact that a collodin-lined surface is wettable and yet retards coagulation.

§It will be noted that the term "thromboplastic activity" is used in preference to "thromboplastin"; this is done because virtually nothing is known of the chemical nature of this moiety. The term "thromboplastic activity" refers to that material, or set of conditions, evolving early in the coagulation sequence, which functions in the conversion of prothrombin to thrombin in shed blood in the presence of calcium and other factors involved in the prothrombin conversion mechanism (for example, accelerator globulin and serum prothrombin conversion accelerator).

thenia, a hemorrhagic state in which the platelets may be normal in number but functionally inadequate.[52,53]

As compared with the erythrocyte and leukocyte, information regarding the platelet is relatively scant. Amazingly little is known concerning such basic matters as their composition, particularly in man. Data are lacking regarding the percentage of water, nitrogen, phosphorus, proteins and so forth. Moreover, virtually nothing is known about their metabolic activity and requirements, if any.

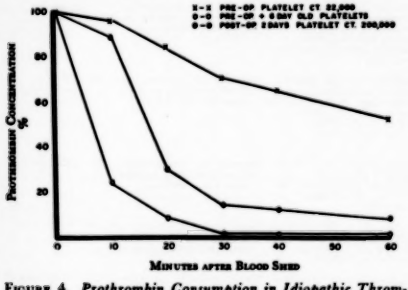

FIGURE 4. *Prothrombin Consumption in Idiopathic Thrombocytopenic Purpura.*

Blood was drawn with Arquad-coated needle and siliconecoated syringe, as described in Figure 2. Aliquots were placed in glass clotting tubes, to which 0.15-molar sodium oxalate was added in usual proportions at specified intervals to stop coagulation. Normal platelets, centrifuged from oxalated plasma, were thrice washed with physiologic saline solution and then resuspended in saline solution and stored at 0-4°C. They were discrete and appeared fairly well preserved morphologically (most of them exhibiting small spicules). This suspension was added in 0.1-cc. amount to 2.0 cc. of the freshly shed thrombocytopenic blood, the mixture giving a platelet count of approximately 200,000 per cubic millimeter.

In an attempt to compare the thromboplastic activity of platelets with that of other tissues, a point still unsettled, it was found that normal human platelets contain approximately 12 per cent nitrogen on a dry-weight basis, each milligram of nitrogen being equivalent to approximately 200,000,000 platelets; unit for unit of total nitrogen, the platelets appear to contain less thromboplastic activity than lung.[54] Preliminary histochemical studies employing recently devised technics indicate that they contain 0.16 unit of acid phosphatase, 0.06 unit of esterase per microgram of nitrogen.[55] They are rich in glucuronidase, but are devoid of lipase, alkaline phosphatase, sulfatase, cholinesterase, carboxypeptidase and chymotrypsin. In the attempt to interpret the data, especially when comparison is made with other tissues, the difficult question arises whether equivalence in nitrogen represents equivalence in total amount of cellular material extracted. Clearly much more study is essential. Moreover, such observations on the platelets under pathologic conditions are even fewer. These considerations are cited to indicate some of the complexities involved, the extent of ignorance and the crying need for further research.

More information is available regarding the physiologic activity of platelets. They contain at least several factors (or activities) important in the coagulation mechanism. Three salient disturbances arise when the platelets are reduced below 20 per cent of normal: the capillaries become extremely fragile; the conversion of prothrombin to thrombin is greatly retarded[52]; and clot retraction becomes poor. These defects can also be induced by removal of the platelets mechanically. It is thus evident that they play a fundamental part in the hemostatic mechanism by serving the integrity of the vascular tree, by furnishing a constituent (or constituents) necessary for prothrombin conversion and by influencing the structural qualities of the fibrin clot. In the last two respects it has been found that platelets that have been carefully separated and washed will maintain their activity at 0-4°C. for at least a week.

That platelets furnish an ingredient (or ingredients) essential for thromboplastic activity, long known, is brought out more lucidly by the thromboplastin generation test.[1,20] Ware et al.[56] have demonstrated that platelets also have an "Ac-globulin-like" activity in addition to their ability to influence the thrombin-fibrinogen interaction. Additional coagulation factors have also been described.[57,58] The mechanism whereby these entities are released from their cellular confines by platelet agglutination and lysis (so-called "viscous metamorphosis") is still not entirely clear.* From recent studies of congenital afibrinogenemic blood[59,60] it is almost certain that the fibrinogen-fibrin system is not involved (contrary to older concepts) and that the phenomenon occurs very early in the coagulation sequence through the action of a small amount of evolved thrombin, acting in conjunction with some plasma constituent (or constituents) as yet unidentified.

Progress has been limited by difficulties in obtaining adequate platelet material for extensive study. This should soon be largely circumvented by recent developments in the design of biomechanical equipment and procedures aimed at complete blood processing in conformity with current knowledge.[61-63] Advances in this area, with the imminent possibility of accumulation and preservation of platelet concentrates as a standard blood-banking procedure, promise to provide a therapeutic tool for thrombopenic purpuras, and have stimulated investigation of platelet types, of in vivo platelet survival and of the effectiveness of platelet transfusions.

Clinical aspects (thrombocytopenic purpura). A notable advance was the demonstration by Harrington and his colleagues,[64] amply confirmed, of a cir-

*It may be recalled that the white thrombus, the "clou hémostatique" of Hayem, consists mostly of such platelets, which pile up at the point of injury in blood vessels (discussed at greater length in the third section of this review). The practical importance of elucidating this mechanism is apparent.

culating antiplatelet factor in the plasma of many patients with idiopathic thrombocytopenic purpura. In accord is the evidence of a much shorter in vivo platelet survival time (sometimes a matter of hours or less) in patients with this disease than in those pearing within three days. With each subsequent infusion into the same recipient, the survival time became progressively shorter until about the fourth or fifth transfusion, when survival was negligible, indicating developing resistance to the infused thrombo-

TABLE 1. *Clinically Significant Clotting Factors* (Synonymy, Properties and Clinicolaboratory Relations).*

COAGULATION PHASE	SUBSTANCE	SYNONYMS	PROPERTIES		APPROXIMATE NORMAL VALUE
			BIOCHEMICAL	PHYSIOLOGIC	
First (thromboplastin formation):	Platelets	Thrombocytes	Formed element; approximately 12% nitrogen; contain phosphatase, esterase, glucuronidase, phospholipids; other poorly defined clotting entities.	Essential for: (1) elaboration of thromboplastic activity; (2) clot retraction; (3) vascular integrity.	150,000 - 250,000 per cu. mm. of blood
	Antihemophilic factor	Antihemophilic globulin, hemophilic factor A, factor VIII, plasmakinin, thromboplastinogen, thrombocytolysin, thromboplastic plasma component	Moderately stable euglobulin; in fraction I; adsorbed on Fuller's earth, not on $BaSO_4$, Seitz filter or Al $(OH)_3$.	Essential for elaboration of thromboplastic activity; consumed in clotting.	60 - 120% of normal mean average
	Plasma thromboplastic component	Christmas factor, hemophilic factor B, factor IX	Stable; plasma fraction III & IV; adsorbed by $BaSO_4$; precipitated by $(NH_4)_2SO_4$>50% saturation.	Essential for thromboplastic elaboration; not consumed in clotting.	60 - 120% normal
	Plasma thromboplastic antecedent	———	Precipitated at 20 - 30% $(NH_4)_2SO_4$; not in fraction I; partly adsorbed by $BaSO_4$.	Essential for elaboration of thromboplastic activity; not consumed in clotting.	?
Second (thrombin formation):	Prothrombin	———	Relatively stable, glycoprotein; fraction III-2; adsorbed by insoluble alkaline earth salts, Seitz filter & Al $(OH)_3$; considerably purified, 2000 units per mg.; almost uniform electrophoretically.	Yields thrombin by interaction with thromboplastin, calcium, accelerator globulin & serum prothrombin conversion accelerator; healthy liver and vitamin K_1 necessary for synthesis; yields thrombin slowly with concentrated citrate & other salts.	70 - 120% normal; 300 - 400 units per cc. of plasma.
	Plasma accelerator globulin ↓ Serum accelerator globulin	Factor V, labile factor, thrombogen, prothrombin A, accelerator factor, cofactor of thromboplastin, plasma prothrombin converting factor, proaccelerin→accelerin	Relatively labile in oxalated plasma, globulin; activated by thrombin; not adsorbed by usual prothrombin adsorbants; fraction III.	Essential for prothrombin conversion by thromboplastin, calcium & serum prothrombin conversion accelerator; consumed in coagulation.	60 - 120% normal
	Proserum prothrombin conversion accelerator ↓ Serum prothrombin conversion accelerator	Stable factor, cofactor V, cothromboplastin, proconvertin→convertin, factor VII, prothrombinogen, prothrombokinase (?)→thrombokinase	Relatively stable; adsorbed by usual prothrombin adsorbing agents; fraction III-2; activated by thromboplastin & calcium, or by aging.	Essential for prothrombin conversion by thromboplastin, calcium & accelerator globulin.	60 - 120% normal
Third (fibrin formation):	Plasminogen ↓ Fibrin	———	Relatively stable globulin, fraction I; M.W. 500,000; highly purified; fairly well characterized.	Thrombin splits off polypeptide; fibrinogen converted to fibrin clot in several steps.	200 - 350 mg. per 100 cc. of plasma
	Plasminogen ↓ Plasmin	Plasma profibrinolysin-fibrinolysin; plasma or serum tryptase (?)	Relatively unstable euglobulin; fraction I; precipitated 25 - 30% $(NH_4)_2SO_4$; isoelectric pH 5.5; about 25% pure.	Fibrinolytic enzyme in plasma; activated by bacteria or tissue, $CHCl_3$ or spontaneously.	?

*Following factors omitted from table because presumably of less compelling clinical significance: certain platelet factors, thrombokinase, antithrombin, antifibrinolysin, heparin cofactor, antithromboplastin and others.

without it.[40,68] In thrombocytopenia secondary to failure of platelet production rather than to excessive utilization or destruction, the platelets of transfused platelet-rich polycythemic blood survived maximally for five or six days, the preponderance disappcytes. In idiopathic thrombocytopenic purpura the initial and subsequent platelet survival times were even less. Added to these somewhat disheartening results are the observations that infusions of processed platelets from normal blood are even more

short-lived, although hemorrhagic phenomena and certain abnormal laboratory features may be temporarily ameliorated without a rise in platelet count.[65,66]

The concept that some immunochemical disturbance underlies the pathogenesis of this disorder has et al.[69] Similar phenomena had been reported by Ackroyd[70] in thrombocytopenia caused by Sedormid sensitivity. Tests for such platelet antibodies appear promising in the differential diagnosis of thrombocytopenia.[32,71]

TABLE 1 *(Concluded).*

COAGULATION PHASE	ASSOCIATED DISEASE	CARDINAL CLINICAL FEATURES	CARDINAL LABORATORY ABNORMALITIES	THERAPEUTIC FEATURES
First (thromboplastin formation):	Thrombocytopenic purpura; thrombasthenia; thrombopathia (? Willebrandt's disease).	Petechiae; purpuric manifestations; bleeding & oozing from skin, mucous membranes, internal organs & brain.	Prolonged bleeding time; increased capillary fragility; poor clot retraction; poor prothrombin consumption.	Primary, steroids & splenectomy; secondary, treatment of underlying disease.
	Hemophilia; partial deficiency; pseudohemophilia.	Heredofamilial sex-linked transmission, affecting males; early joint, muscle & mucous-membrane traumatic bleeding.	Prolonged clotting time; poor prothrombin consumption.	Corrected by blood, plasma, potent fraction I & local thrombin
	Deficiency of plasma thromboplastic component (Christmas disease, hemophilia B)	Same as hemophilia though milder	Same as in hemophilia; normal serum corrects deficiency of plasma thromboplastic component but not hemophilia.	Corrected by blood, plasma, or serum, or local thrombin, not by fraction I
	Deficiency of plasma thromboplastic antecedent	? Both sexes; bleeding from skin & mucous membranes.	Slightly prolonged clotting time; poor prothrombin consumption.	Corrected by blood & plasma, not by fraction I
Second (thrombin formation):	True hypoprothrombinemia; biliary disease; liver disease; sprue; hemorrhagic disease of newborn; coumarin drug poisoning.	Subcutaneous, cutaneous & mucous-membrane bleeding; affected by coumarin drugs & vitamin K_1 deficiency.	Prolonged 1-stage prothrombin time; low 2-stage value.	Blood, plasma, vitamin K_1; improvement in liver function.
	Parahemophilia (accelerator-globulin deficiency, hypoaccelerinemia, pseudohypoprothrombinemia), congenital or acquired	Same as hypoprothrombinemia; not affected by coumarin drugs or by vitamin K_1.	Prolonged bleeding & 1-stage prothrombin time; retarded 2-stage thrombin elaboration; poor prothrombin conversion; low accelerator-globulin activity; normal serum prothrombin conversion accelerator.	Transfusion of fresh blood or plasma; improvement in liver function.
	Deficiency of serum prothrombin conversion accelerator (hypoproconvertin, hypoproconvertinemid, pseudohypoprothrombinemia), congenital or acquired; hemorrhagic disease of newborn; coumarin poisoning; ? thrombotic disease in pregnancy.	Same as hypoprothrombinemia & accelerator-globulin deficiency; affected by coumarin drugs & vitamin K_1.	Prolonged clotting & 1-stage prothrombin times; normal 2-stage prothrombin; normal accelerator-globulin; low serum prothrombin conversion accelerator; high serum prothrombin conversion accelerator in pregnancy.	Transfusion of blood, plasma or serum; vitamin K_1; improvement in liver function.
Third (fibrin formation):	Afibrinogenemia & hypofibrinogenemia, congenital or acquired; complications of pregnancy; cancer of pancreas, prostate & stomach.	Similar to hemophilia; heredofamilial, both sexes; also acquired.	No clot or retarded clotting; prolonged 1-stage prothrombin time; low to absent plasma fibrinogen.	Blood, plasma or fraction I
	Complications of pregnancy; cancer of pancreas, prostate & stomach; shock; anoxia.	Similar to hemophilic bleeding	Same as above; rapid clot lysis.	Same as above

attracted more and more adherents in parallel with accumulating evidence of platelet agglutinins demonstrable in the plasma.[32,67,68] In approximately half the cases such agglutinins are said to be demonstrable, extending the original observation of Evans

It now becomes necessary to rescrutinize, and perhaps revise, current concepts implicating "hypersplenism" or disturbed megakaryocyte maturation and platelet production in the etiology of purpura. It is difficult to reconcile the substantial evidence for

excessive agglutination and destruction of platelets caused by circulating antibodies originating from some immunochemical aberration, with the theory, so long and loudly proclaimed as to have been accepted by many as fact, that in this disorder platelet production from marrow megakaryocytes was depressed and inadequate because of a diseased spleen.

From the foregoing, it is evident that this whole area is in a state of flux. Progress has as yet been insufficient to exert a profound influence on current diagnostic and therapeutic methods.[72] Nevertheless, a clearer understanding of this disorder and better clinical management may be anticipated. It must be admitted, however, that the presence of circulating thrombocytopenic factors and the short platelet survival time, which progressively shrinks with each transfusion, are discouraging to the view that platelet replacement therapy can offer anything in thrombopenic states except a temporary alleviation of hemorrhagic phenomena. The physician must also realize that very few hospitals can provide transfusions with platelet-rich blood, to say nothing of platelet concentrates. The possibility, furthermore, of inducing or exaggerating already existing antiplatelet agglutinins by repeated platelet infusions (analogous to antierythrocyte incompatibilities) deserves serious consideration when such therapy is contemplated.[33]

In this connection the similarity between the thrombocytopenias and the hemolytic anemias is of interest, particularly in view of the frequent occurrence of acute thrombocytopenia in the neonatal period. This has been attributed to platelet group incompatibility.[67] Platelet typing and matching is on the horizon. Until further clarification, the physician is well advised to recommend as few transfusions as possible in the thrombocytopenias.

The advent of steroid therapy constitutes a welcome addition to the therapeutic armamentarium.[73-78] The importance of a vascular defect occurring in idiopathic thrombocytopenic purpura concurrently with decreased platelet number, as well as its relation to adrenocortical activity, was amplified by observations that the steroid hormones improve the vascular fragility associated with all the thrombocytopenias, regardless of etiology. In many cases (perhaps 30 per cent) the platelet count also increases under adequate ACTH or cortisone therapy. In some subjects this persists after discontinuation of the medication, but in the majority, unfortunately, relapse occurs. The physician should therefore use steroids only as a means of preparing the patient for more definitive treatment, such as splenectomy, except when splenectomy has already failed or is contraindicated. Hormonal therapy appears more clearly indicated in children, in whom spontaneous recovery occurs more often than in adults, and in whom splenectomy should be reserved for uncontrolled bleeding or for very chronic or recurrent purpura.

Thrombasthenia. Reference was made above, in the discussion of the basic aspects of platelets, to qualitative platelet abnormality, which may occur despite normalcy in their number. A thrombasthenic condition has been reported in which clinical bleeding simulating that of thrombocytopenic purpura was associated with poor prothrombin consumption in a patient whose platelet count was normal.[52] The patient's platelets could not rectify the poor prothrombin consumption of thrombocytopenic blood, whereas normal platelets corrected the clotting defect. While under observation the patient progressed to typical thrombocytopenic purpura, and was cured by splenectomy. This raised the question of whether thrombocytopenic purpura may be preceded by a short interval when the platelets are normal in number but functionally inadequate.

Similarly, a dissociation between platelet number and the clot-retraction function of platelets has been reported, associated with hemorrhagic phenomena,[79] as well as dissociation between prothrombin consumption and clot retraction.[80] These observations provide additional evidence for the existence of multiple platelet factors and at the same time emphasize the importance of considering the qualitative aspects of platelets.

Antihemophilic Factor (Hemophilia)

Another of the elements required for thromboplastic activity is the factor presumably missing, deficient or defective in hemophilia, the antihemophilic factor. Of the known coagulation substances, knowledge in this instance derives more from clinicolaboratory study of the diseased states than of the normal. Very recently, a published symposium by many authorities was devoted to the question, "What is Hemophilia?"[81] Despite many attempts to answer this question, it remains an enigma.

Every advance has added complexity to the limited knowledge of this complex hemorrhagic disorder, recognized since antiquity. Whereas until recently hemophilia was considered a single clear-cut hereditary disease, recessive and sex linked, limited to males and transmitted by females, with a characteristic clinical picture, new developments have indicated that this definition now includes at least one other bleeding disorder differing clearly, if only subtly, from the classic disease. Also now recognized are patients with mild and latent hemophilia, acquired (nonhereditary) forms of "hemophilia" and, in addition, many cases of hemophilialike (hemophilioid) disease. These advances, moreover, pose problems in nosology and terminology.

Although there is still controversy concerning the underlying defect in hemophilia, whether it is deficient antihemophilic factor, excessive antithromboplastin (clotting inhibitor) or a combination of the two, there is no question about a factor in normal plasma that corrects the clotting defect of hemophilic blood. Largely because of technical difficulties in assay, extensive knowledge of its properties is wanting. It is a euglobulin and is concentrated in

fraction I of plasma together with although clearly distinct from fibrinogen (Table 1).[59] It is not adsorbed by the usual agents that remove prothrombin and certain other coagulation factors. It is consumed very early in coagulation, and its precise role and fate in this connection is still obscure.[59]

Presumably, it is essential for the formation of thromboplastic activity in shed blood by interaction with platelets since in conditions in which deficient or defective activity of antihemophilic factor is found, thromboplastin generation is reduced, leading to poor prothrombin conversion. The various labels assigned to this clotting factor (thromboplastinogen,[82] thrombocytolysin,[83] thromboplastic plasma component[84]) reflect its postulated function of interacting with platelets or of inducing platelet lysis. It should be emphasized, however, that there is little direct evidence to support these concepts. I have repeatedly been unable to demonstrate a thromboplastic product arising from interaction between platelets and plasma fraction I, rich in antihemophilic factor, when these were brought together.* Perhaps other recently disclosed factors (plasma thromboplastic component and plasma thromboplastin antecedent) are the significant agents in this regard.

Many years have elapsed since it was demonstrated that antihemophilic factor could be concentrated in certain plasma fractions.[86-89] Unfortunately, the early optimism that a therapeutic advance for hemophilia was impending has not been realized. In my experience the antihemophilic potency of many of these fractions in relation to normal plasma has been poor[90]; I have yet to encounter a sample of fraction I from commercial or other source (except experimental) that compares favorably with whole plasma. It is tempting to attribute this to inherent lability of antihemophilic factor, frequently claimed in the literature, but based on very scant evidence.

Recent experiments indicate that when blood is carefully collected it maintains full potency under routine blood-bank conditions for at least three weeks. I also know from recent tests in this laboratory† that antihemophilic factor can withstand ultraviolet radiation and lyophilization. The disappearance of this factor during coagulation and its inactivation by thrombin[59] suggest that the relative impotency of many specimens of stored blood and plasma, plasma fractions and most dried-plasma preparations, may be attributable to antihemophilic-factor consumption or destruction, or both, by thrombin resulting from faulty technic of anticoagulation and processing. Obviously, more information is necessary regarding the stability of this factor under various conditions before it can be routinely and economically obtained from plasma.

(To be continued)

*Most recently, it has been postulated that thromboplastinogen must be activated, presumably by thrombin, before it will interact with platelets to yield thromboplastin.[85]

†At least six different batches of dried irradiated plasma from Hyland Laboratories exhibited full antihemophilic potency. They also contained approximately 50 per cent of normal prothrombin, accelerator globulin and serum prothrombin conversion accelerator.

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MEDICAL INTELLIGENCE

FLUIDS FOR PARENTERAL ADMINISTRATION*

A Simple Method of Modification to Fill the Requirements of the Individual Patient

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PARENTERAL fluid therapy for severely ill patients is often not optimal because solutions of the correct composition are not available. For example, in treating a patient with renal shutdown the physician may wish to limit the fluid intake to 1 liter of water in a twenty-four-hour period. To provide calories it may be desirable to administer 1 liter of 10 per cent, 20 per cent or even 50 per cent dextrose, with the possible addition of 100 cc. of ethyl alcohol. Also, because the patient may be in severe acidosis, 100 to 200 milliequiv. of sodium lactate may have to be provided. Since there is no simple method of compounding 1 liter of fluid for parenteral administration with this composition, the physician usually compromises and gives 1 liter of one-sixth molar sodium lactate, which does not provide the necessary calories.

This is but one example of how the physician is forced to modify what he considers the best plan of treatment because solutions of the proper composition are not usually available. A simple, workable system is needed whereby fluids of any desired composition can be administered. This communication describes a system for providing the needed flexibility in the composition of fluids for parenteral administration. This system is based on the use of a series of additive solutions that have been made available in small sterile containers. These solutions, whose volume and composition are shown in Table 1, may be poured directly into any bottle of standard solution that has a removable cap, thereby modifying its composition in almost any desired manner. Transfer of the additive solution is facilitated by a sterile neck on the small additive bottle that is rested on the rim of the bottle containing the solution for parenteral administration (Fig. 1).

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The question arises whether this technic may permit bacterial contamination. Bacteriologic tests have revealed that the neck of the additive bottle remains sterile until the seal is broken. Perhaps more to the point is the observation that thousands of additive bottles have been used to modify fluids in the course of routine parenteral therapy over the past two years and no case of reaction has been noted from any bottle of fluids for intravenous use to which additive solutions have been transferred.

Despite this favorable report it is recommended that when additive substances are used to modify fluids for parenteral administration the fluids themselves should be given promptly to avoid the chance of bacterial growth and pyrogen development. This precaution applies particularly to solutions of protein hydrolysates.

TABLE 1. *Composition of Additive Solutions.*

SUBSTANCE	TOTAL AMOUNT	VOLUME
	milliequiv.	*cc.*
Sodium chloride	50	20
Sodium chloride	100	40
Potassium chloride	20	20
Potassium chloride	40	20
Potassium phosphate (pH 7.4)	40	20
Sodium lactate	50	20
Sodium lactate	100	40
Ammonium chloride	100	40
Sodium bicarbonate	20	20
Calcium gluconate-glucoheptonate	20	40
Dextrose	(20 gm.)	40
Fructose	(20 gm.)	40

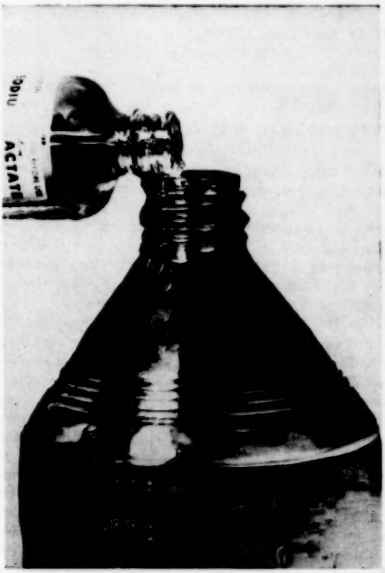
When the composition of fluids is being modified the following principle should be kept in mind: the composition should be adjusted so that the daily requirement of each substance is infused at as low a concentration as possible. For example, if the total dose of potassium for a therapeutic period is to be 80 milliequiv. and 4 liters of fluid is to be given, 20 milliequiv. of potassium should be put in each of the 1-liter containers rather than 40 milliequiv. in only two of the containers.

There are no absolute limits on the maximum safe concentration of most substances in fluids for parenteral use since rate of administration alone can determine how rapidly the substances enter the body. A solution of 50 per cent dextrose and 10 per cent ethyl alcohol containing 300 milliequiv. of sodium lactate per liter has been given intravenously. The principal limiting factors are pain at the infusion site and sclerosis of the veins. However, definite limits should be placed on the maximum concentration of potassium and alcohol; the former should be limited to 40 milliequiv. per liter and the latter to 10 per cent. These

limits ensure that no one will inadvertently open the pinch clamp of a bottle containing a slowly running fluid and allow potassium or alcohol to enter at a dangerous rate.

In preliminary trials the additive solutions listed in Table 1 have proved useful in helping to modify the plan of parenteral therapy to fit the needs of the individual patient.[1] Although the solutions can prove valuable in any case requiring parenteral infusion of fluids, several special applications should be mentioned.

A



B

FIGURE 1. *Modification of Container for Parenteral Administration.*
A *shows the special seal on the additive bottle, which is easily removed, exposing the sterile neck, and* B *the sterile neck resting on the rim of the bottle as the solution is poured in.*

POTASSIUM THERAPY

It is particularly important that potassium be given in the lowest possible concentration to avoid cardiotoxic effects; therefore, the daily dose should be divided equally among all the bottles, to be given in a twenty-four-hour period. This cannot be conveniently accomplished with ready-made solutions. Ampoules of potassium chloride that require syringe transfers are cumbersome. One can easily solve the problem by pouring all or part of the contents of 20-milliequiv. or 40-milliequiv. additive bottles of potassium chloride directly into the liter bottles of fluid for parenteral use.

TOTAL PARENTERAL FEEDING

A reasonable approach to the difficult problem of achieving the adequate caloric and nitrogen intake required in total parenteral feeding is to proceed as follows: to use a continuous twenty-four-hour infusion and employ a plastic needle, or a polyethylene catheter; to determine how much water the patient will require during the twenty-four-hour period; and to ascertain the twenty-four-hour requirement for each substance — for example, glucose, alcohol or potassium — and divide this amount equally in the total volume of water to be given. For example, if a patient can tolerate no more than 3 liters of water in a twenty-four-hour period and it is desired that he also receive 450 gm. of glucose, 200 cc. of 95 per cent ethyl alcohol,[2] 150 gm. of protein hydrolysate, 100 milliequiv. of potassium chloride and 150 milliequiv. of sodium lactate, each liter of fluid ideally should contain approximately 150 gm. of glucose (15 per cent), 70 cc. of 95 per cent ethyl alcohol (7 per cent), 50 gm. of protein hydrolysate (5 per cent), 35 milliequiv. of potassium chloride and 50 milliequiv. of so-

dium lactate. No solution available at present approaches this composition. However, if one starts with 3 liters of a 5 per cent amino acid solution in 10 per cent dextrose as a basic solution, the additive solutions can be used to approximate quickly the ideal composition. By pouring from additive bottles one can add to each liter 100 cc. of 50 per cent dextrose, 70 cc. of ethyl alcohol,* 40 milliequiv. of potassium chloride and 50 milliequiv. of sodium lactate.

Acute Renal Failure

Strict limitation of fluid intake, to ensure 0 or even negative water balance, as well as a high-calorie intake, is an accepted principle of therapy in the oliguric phase of acute renal failure.[3] It is at best difficult to follow these principles, particularly when only ready-made solutions are used parenterally. For example, in a patient with acute renal failure who also suffered from severe acidosis and hyponatremia, the therapy decided on for an eighteen-hour period was 500 cc. of 20 per cent dextrose containing 50 cc. of ethyl alcohol and 300 milliequiv. of sodium lactate; it would have been virtually impossible to compound such a solution if the additive substances had not been available.

There are many other clinical situations in which the additive system should prove valuable, particularly in pediatric practice. To facilitate broader application, the list of additive solutions will undoubtedly have to be expanded.

Summary and Conclusions

Parenteral fluid therapy often falls short of its therapeutic objectives because of difficulties involved in obtaining solutions of the correct composition. An additive bottle system that allows quick preparation of solutions of almost any desired composition is described. This system permits the physician to alter the composition of fluids for parenteral use to fit the specific needs of the patient.

*Federal law prevents tax-free dispensing of ethyl alcohol in additive bottles. Therefore, freshly opened 95 per cent ethyl alcohol obtained through regular hospital channels is used.

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CASE RECORDS
OF THE
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Weekly Clinicopathological Exercises

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CASE 41111

Presentation of Case

A forty-six-year-old Cuban physician was admitted to the hospital because of hemoptysis.

The patient's general health had always been good except for bronchopneumonia thirteen years and infectious hepatitis nine years previously. About a month before admission he began to cough up increasing amounts of bright-red blood that he thought could have been emanating from his throat. There were no associated symptoms. A cytologic examination of the sputum done in Cuba was positive for tumor cells.

There was no story of pleurisy, weight loss or anorexia. He was a cigarette smoker of thirty years' duration and smoked about a package and a half a day.

Physical examination showed a thin, well developed man who periodically coughed up bloody sputum. The chest exhibited some dullness, absent breath sounds and decreased tactile and vocal fremitus over the right midposterior portion of the thorax. The heart was normal to percussion and auscultation. The abdominal, rectal and genital examinations were noncontributory.

Urinalysis was negative. Examination of the blood revealed a hemoglobin of 13.8 gm. per 100 cc., a white-cell count of 9100, with 69 per cent neutrophils, 22 per cent lymphocytes, 5 per cent monocytes, 3 per cent eosinophils and 1 per cent basophils, and a prothrombin time of 60 per cent. An electrocardiogram was interpreted as normal. On x-ray examination of the chest the right upper lobe appeared to be replaced by blebs (Fig. 1). Some increased density was observed in what seemed to be the region of the superior segment of the right lower lobe. The basilar portions of the middle and lower lobes were of normal density. There was no evidence of mediastinal shift or enlarged lymph nodes. A review of x-ray

films of the chest taken at another hospital a few weeks before admission revealed a 2-cm., rounded shadow of increased density lying between large blebs at the apex of the right lung. In addition a zone of increased density in the area of the upper portion of the right lower lobe was noted. The emphysematous blebs were said to have been seen two years before admission in a film taken for examination of the shoulder.

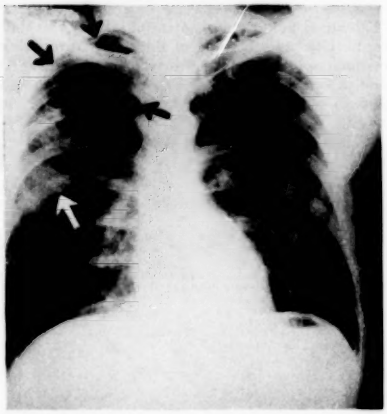

FIGURE 1. *Posteroanterior View of the Chest, Showing Extensive Emphysema in the Right-Upper-Lung Field, with Large Bleb Formation (Black Arrows).*

Below the large blebs there is an area of relative homogeneous increased density (white arrow) that, from the lateral view, was thought to lie in the superior segment of the right lower lobe. The 2-cm. density lying between large blebs in the upper lobe is not adequately shown in the film.

On the second hospital day bronchoscopy revealed that the orifice of the right-upper-lobe bronchus was displaced downward so that the subdivisions of the bronchus were well visualized. These all appeared normal. The orifices of the branches to the middle and lower lobes likewise appeared normal. Saline washings from the right upper lobe, submitted for cytologic study, were reported as "doubtful" for tumor cells. On the fifth hospital day an operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. LAMAR SOUTTER*: The patient "coughed up bloody sputum." I think that this sentence negates the patient's own statement that he thought the blood was coming from his throat.

". . . a prothrombin time of 60 per cent." This prothrombin deficiency might be correlated with the hepatitis that he had nine years previously and might indicate diminished liver function. It certainly could have been responsible for the continued bleeding. One wonders whether it was correctable by the administration of vitamin K, and if so, if the amount of blood in the sputum diminished.

". . . the orifice of the right-upper-lobe bronchus was displaced downward so that the subdivisions of the bronchi were well visualized." A bronchus may be displaced downward if there is a collapse of the middle or lower lobe or if emphysematous blebs push the upper lobe downward. This is not unusual. This finding is important from the point of view that the orifices of the secondary bronchi were well seen and all appeared to be normal.

DR. C. C. WANG: There are multiple radiolucent defects in the right-upper-lung field chiefly in the right upper lobe. These defects are surrounded by sharply delineated, delicate white lines and have the appearance of large blebs, the largest of which measures approximately 10 cm. in greatest diameter. There appears to be an area of homogeneously increased density in the superior segment of the right lower lobe (Fig. 1); the right middle and the basilar segments of the right lower lobe appear clear. There is nothing unusual in the left-lung field. The barium-filled esophagus shows a normal course in the mediastinum. No evidence of mediastinal adenopathy is noted. Both leaves of the diaphragm lie in normal position. I cannot see a definite soft-tissue mass within the lung. The cardiac shadow is not abnormal. Unfortunately, the films taken elsewhere that were reported to show an area of increased density in the right apex are not available for review.

DR. SOUTTER: This is a very intriguing problem. The patient was a man early in the cancer age who had cystic changes in the lung noted on roentgenographic examination and who was raising bloody sputum. The essential problem is the differential diagnosis of hemoptysis and cysts of the lung. There are a number of things to consider. I might go over the infectious diseases first. Whenever there is hemoptysis associated with changes in the appearance of the lung, one of the first things we have to consider is tuberculosis. He did not have a clinical history suggestive of active tuberculosis, for he was well. There was no history of fever, malaise or night sweats. The small areas of increased density in the films do not resemble those seen in tuberculosis. On the other hand tuberculosis cannot be excluded. I imagine that, during the course of the preoperative work-up, sputum examinations for acid-fast bacilli were done. They were not recorded, probably because they were completely negative.

Besides tuberculosis diseases such as coccidioidomycosis produce cysts. He did not come from a district in which coccidioidomycosis is endemic. The cystic appearance was quite different from that seen in coccidioidomycosis. Also, he was not sick enough to

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suggest it. Monilia, blastomycosis and actinomycosis produce cysts at times, but we should expect an acute inflammatory reaction to them, which was missing in this man. Certain chronic pulmonary infections have a cystic appearance and can be associated with emphysematous blebs. Bronchiectasis with bronchiectatic cysts could produce such a picture. Bronchiectasis is a common cause of hemoptysis. There was a history of pneumonia thirteen years previously, and he had had blebs for some time. He did not give a history suggestive of acute infection caused by bronchiectasis of the right upper lobe, but the type of bronchiectasis that results from old tuberculosis of an upper lobe and occasionally bleeds sometimes causes no other symptoms because of the good dependent drainage of the bronchiectatic areas. Hemoptysis is what brings it to our attention. That is a possibility, but not a likely one. He could, of course, have been bleeding from an area of pneumonitis with or without bronchiectasis. I shall temporarily dismiss infections and go on to the problem of the cysts themselves.

We note the appearance of pulmonary blebs. These were at one time thought to be caused by tuberculosis. We know now that they are usually associated with emphysema. Whether the emphysema is confined to a single lobe or not does not make a great deal of difference. I can state definitely that this patient had bullous blebs probably on an emphysematous basis. In addition there was a single cystic area in the right-upper-lung field. The story that there was an area of increased density in that region that subsequently disappeared suggests that this cyst was once filled with fluid or solid matter and then emptied itself, when the bleeding began. Could this have been a congenital cyst? The congenital cysts are usually found in much younger patients, are commonly single, are sometimes trabeculated, are rounded, are usually close to the hilus and are often filled with fluid. They seldom extend to the lung periphery unless they are very large. They are rarely associated with bleeding. I should expect that the cystic area seen on the x-ray film, which is the only area that could possibly have been a congenital cyst, is too irregular in shape to be one.

Acquired cysts are of two general types, those caused by parasites and those caused by a breakdown of tissue. Among the parasitic types, we should think of echinococcal cysts, which are not often seen in Cuba. The echinococcal cyst is usually symmetrical, owing to the fact that as it enlarges, the soft, yielding lung tissue permits it to extend evenly in all directions. The spontaneous emptying of such a cyst, however, causes a marked anaphylactic and febrile reaction of which there was no history in this patient's record. We should expect an elevated eosinophil count with a parasitic infection, particularly with echinococcal disease. The patient had an eosinophil count of only 3 per cent. I think I can dismiss echinococcosis. Lung flukes, which are common in the Orient and about whose existence in Cuba I do not know, are associated with a tunneling appearance in the lung. The patient is usually very sick with that infestation and brings up a so-called "anchovy" type of sputum. It seems reasonable to dismiss parasitic cysts and go on to the breakdown of tissue due to chronic infection or tumor.

Could any of these cystic areas actually have represented an acute or chronic lung abscess? The history rules out an acute lung abscess. A chronic lung abscess without an antecedent history of a severe, acute pulmonary infection is possible, the reason being that in people who take antibiotics for colds and so forth a chronic lung abscess can develop with little evidence of a preliminary acute process. This is unusual, however, and the sputum, malaise and other symptoms associated with a chronic lung abscess were not present in this case.

Could he have had a bronchogenic carcinoma? The way the history was written suggests that that possibility was in the mind of everyone. He smoked a package and a half of cigarettes a day for thirty years, from the age of sixteen. Whether he was a heavy smoker or not depends on one's viewpoint, but certainly he was a persistent one. There probably is some relation between heavy smoking and carcinoma of the lung, because the prevalence of heavy smokers is proportionally much greater among patients with carcinoma of the lung than in the population at large.

Of what importance are the cytologic studies? We are apt to discount cytologic studies sometimes because of the rare false-positive and the fairly frequent false-negative reports. The doubtful ones usually occur when patients have a considerable desquamation of cells because of infection. I should expect that this patient, who had areas that looked like pneumonitis on the roentgenogram, had some degree of infection. I cannot altogether overlook the cytologic studies; they do influence me to some degree.

Bleeding from a tumor in a man of this age is sometimes associated with a bronchial adenoma. The cylindroid adenomas usually appear in the trachea, but rarely in the bronchus. The carcinoid adenomas usually appear in a main-stem bronchus. In the series reported from this hospital[1] a fifth were found in secondary bronchi. In this location a small tumor may escape the attention of the most observant bronchoscopist. These tumors cannot often be seen on a roentgenogram.

Dr. Laurence L. Robbins has made the point that when there has been no overlying density, owing to infection, collapse and so forth, one can usually see a shadow suggesting bronchial adenoma lying in a bronchus by taking an overexposed posteroanterior Bucky film. We have such a film here, but can see no shadow that suggests the presence of an adenoma.

If this patient had a carcinoma it must have lain peripherally beyond bronchoscopic observation. Could it have been a peripheral carcinoma that had necrotized in its center, the necrotic material being coughed up and leaving a cystlike shell? I saw such a carci-

noma in the apical portion of the left lung a year ago at the Boston Veterans Administration Hospital. The carcinomatous cyst resembled a tuberculous or coccidioidal cavity without any element of surrounding inflammation in the lung tissue itself. It was difficult to believe that the lesion was a carcinoma, until we obtained pathological proof at operation. I think this is a likely possibility. In favor of cancer are the lack of a history of inflammatory disease, one Papanicolaou smear positive for tumor and the persistent bleeding from the lung, as well as the cystlike shadows in the films, one of which was not unlike an evacuated carcinomatous abscess or cyst. Therefore, I should like to say that this man had emphysematous blebs, chronic pneumonitis and carcinoma of the lung.

It does not make a great deal of difference in these cases what diagnostic conclusion is made provided one handles the patient's problem properly. It might have been possible to have stopped the bleeding by correction of the prothrombin deficiency and by administration of antibiotics, with relief of presenting symptoms, but the underlying disease would have remained undetected. The important point in this case is that the physician in charge did not overlook the likelihood that carcinoma may have been present and took appropriate action without delay.

DR. EDWARD B. BENEDICT: There was some blood in the right-main-stem bronchus opposite the right-upper-lobe orifice at the time of the bronchoscopy, which would confirm that the bleeding was definitely coming from that area.

DR. SOUTTER: That is a very important point in demonstrating the connection between the hemorrhage and the apparent lesion seen on the roentgenogram.

CLINICAL DIAGNOSIS

? Carcinoma of right upper lobe of lung.

DR. LAMAR SOUTTER'S DIAGNOSES

Carcinoma of lung.
Emphysematous blebs.
Pneumonitis.

ANATOMICAL DIAGNOSES

Adenocarcinoma, Grade 3, of lung, right apex.
Emphysema, severe, with bleb formation.

PATHOLOGICAL DISCUSSION

DR. WINFIELD S. MORGAN: As was expected there were cystic emphysematous blebs occupying most of the apical portion of the right upper lobe; these measured up to 7 cm. in greatest diameter. Lying between the walls of two of the cysts was a firm, whitish area, which measured 3 cm. in greatest diameter. Although microscopically this consisted chiefly of dense hyaline connective tissue, possibly representing old healed tuberculosis, there was also a definite well differentiated adenocarcinoma. The bronchi and bronchioles were carefully examined, and although they gave evidence of bronchiectasis no definite point of origin of the tumor in the bronchial system could be found. There was no pneumonitis, nor were there metastases in any of the lobar lymph nodes.

DR. BENJAMIN CASTLEMAN: I want to emphasize the fact that this lesion was not an example of the alveolar epithelization or bronchial metaplasia that is often seen near inflammatory reactions in lung; it was a clear-cut carcinoma.

DR. WILLIAM H. BAKER: I wonder if Dr. Soutter would consider a lobectomy an adequate operation in view of the subsequent findings. Some physicians think that the only operation to do under those circumstances is a pneumonectomy.

DR. SOUTTER: In this hospital we have always been interested in the preservation of lung tissue. If the tumor was confined to the right upper lobe and was removed entirely, with an adequate margin of normal tissue, the operation was adequate. The removal of normal lung or of large numbers of lymph nodes, whether they are negative or contain carcinoma, has little effect on the ultimate course of the disease. In the series of patients studied at this hospital[2] the five-year survival rate after lobectomy has been as good as or slightly better than that after pneumonectomy.

A PHYSICIAN: Was the bleeding coming from the tumor?

DR. MORGAN: I do not know whether we can definitely answer that because there was also a severe bronchitis and bronchiolitis. The sections showed a severe chronic bronchitis, with loss of epithelium and replacement by granulation tissue, and these changes were seen some distance from the tumor.

In concluding I should like to clarify what we believe was the sequence of events in this patient. It seems most likely that he had had tuberculosis in the upper lobe many years previously and that this infection had healed and with scarring had constricted the bronchial tree leading to an area of cystic bronchiectasis. It is very likely that the bronchiectasis accounted for some of the pulmonary symptoms in the past. In addition apparently developing in the scarred area was a tumor. Just what relation, if any, this may have had to the bronchiectasis we are unable to say.

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CASE 41112

Presentation of Case

A sixty-four-year-old chambermaid was admitted to the hospital because of shortness of breath and fatigue.

Eight weeks previously the patient "took a chill" and felt quite weak during the next few days. Then she noted the gradual onset of exertional dyspnea and fatigue, which became much worse four weeks before admission, and were associated with a feeling of pressure high in the interscapular area. This radiated into the right subscapular region, usually had its onset when she lay down and recurred almost every night. She was able to continue working. Two weeks before admission a physician prescribed capsules, which did not alleviate the symptoms. The dyspnea and weakness became steadily worse, and she was unable to work during the week before admission, being so incapacitated that she was not able to walk two blocks without severe dyspnea. Though she denied ankle edema and orthopnea, she had been awakened several times from sleep with sudden shortness of breath.

There was no history of previous heart trouble, but she had had a mild, nonproductive cough. She had noted anorexia and mild constipation for several weeks, and had been aware of hemorrhoids for several months, with occasional, bright-red blood coating the stool. There were a few questionably dark stools. Nocturia (once or twice) had been noted.

Physical examination revealed a well developed, well nourished, apprehensive woman with moderate pallor. There were no enlarged lymph nodes. A few faint inspiratory squeaks were heard over both lung fields. A sinus tachycardia (rate of 108) was noted, and the heart was of normal size, no murmurs being audible. The aortic second sound was louder than the pulmonic. There was slight tenderness and a sense of resistance in the epigastrium; the abdomen was otherwise normal. Rectal examination revealed a few external hemorrhoids and a small amount of stool flecked with dark-red blood in the rectal ampulla. The extremities were normal. Neurologic examination was unrevealing.

The temperature was 101°F., the pulse 108, and the respirations 22. The blood pressure was 164 systolic, 90 diastolic.

A cloudy, amber urine with an acid reaction had a specific gravity of 1.015 and gave a ++ test for albumin; the sediment was loaded with red cells, had 4 epithelial cells per high-power field and contained mucin. Examination of the blood showed a hemoglobin of 5.8 gm. per 100 cc. and a white-cell count of 17,900, with 78 per cent neutrophils, 2 per cent eosinophils, 14 per cent lymphocytes and 3 per cent monocytes with 3 per cent young neutrophils. The platelets were normal, and the red cells showed some variation in size and slight polychromasia. The nonprotein nitrogen was 23 mg., and the fasting blood sugar 136 mg. per 100 cc. A blood Hinton test was negative. A guaiac test on a brown stool specimen was +. An electrocardiogram was slightly abnormal; nonspecific T-wave changes were thought possibly to be the result of coronary-artery disease. Posteroanterior and lateral roentgenograms of the chest showed diffuse mottled and linear densities in both lungs, although the process was much more severe in the left lung (Fig. 1). Enlarged lymph nodes were

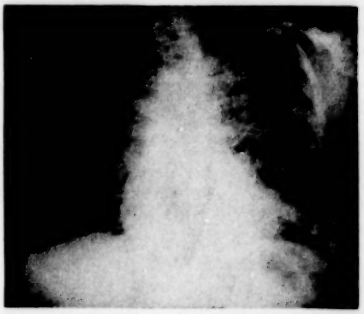

Figure 1. *Posteroanterior Roentgenogram of the Chest. There are diffuse granular and linear densities in both lungs, more marked on the left. There is also evidence of enlarged lymph nodes in the superior mediastinum and in the lung roots.*

noted in the paratracheal and mediastinal areas bilaterally. The heart was at the upper limits of normal size. There was no definite pleural effusion, though minimal blunting of the right costophrenic sulcus was observed.

On the second hospital day the hemoglobin was 6.6 gm. per 100 cc., the red-cell count 2,330,000, and the hematocrit 23 per cent. The mean corpuscular volume was computed to be 99 cubic microns (normal, 80 to 94 cubic microns), the mean corpuscular hemoglobin 29 micromicrogm. (normal, 27 to 32 micromicrogm.), and the mean corpuscular hemoglobin concentration 29 per cent (normal 33 to 38 per cent). A prothrombin time was 38 per cent of normal. Urinalysis revealed a ++ test for albumin and 150 red cells, 6 white cells and 3 epithelial cells per high-power field in the sediment. A catheterized urine specimen on smear and culture yielded no organisms. At sigmoidoscopy the scope was passed for 25 cm. without difficulty. A large ring of hemorrhoids was noted, but no other abnormality was discovered. The fever and dyspnea persisted. After administration of 1000 cc. of packed red cells the hemoglobin rose to 9.4 gm. per 100 cc.

On the morning of the fourth hospital day, after a "bad" night, the patient was sweaty, orthopneic and wheezing. Rhonchi and wheezes were found throughout the chest, but were more apparent on the

right than on the left. The pulse was regular at a rate of 88. There was no venous distention in the neck. An intravenous pyelogram demonstrated that the renal outlines were not too well defined, largely because of breathing during exposures. The right kidney was perhaps slightly smaller than normal. The left kidney appeared to be somewhat enlarged at its lower pole. Both kidneys excreted dye promptly in good concentration. The calyxes on the right were clustered rather closely together. On the left there was a spreading of the middle and inferior calyxes, suggesting the presence of a mass (Fig. 2). The hemoglobin was 8.8 gm. per 100 cc. Blood determinations revealed a calcium of 10.4 mg., a phosphorus of 4.7 mg. and an alkaline phosphatase of 2.7 units per 100 cc.

FIGURE 2. *Detail View of a Pyelogram, Showing Distortion of the Pelvis and Calyxes of the Left Kidney by a Mass (Arrows) in the Lower Pole of the Kidney.*

On the seventh hospital day cystoscopy was negative. Bilateral retrograde pyelography showed a filling defect in the left kidney. No bloody urine was seen coming from the left ureter. A cytologic smear of voided urine was negative for tumor cells. A vaginal examination revealed a prolapse of the uterus but no pelvic or rectal masses.

On the eighth hospital day, the patient was less responsive, and the temperature rose to 103.4°F. Administration of antibiotics was begun. The hemoglobin was 8.4 gm., and the nonprotein nitrogen 28 mg. per 100 cc., and the prothrombin time 31 per cent of normal. A chest film showed a slightly greater degree of solidification of the upper portion of the left lung. Mottled densities were noted in the lower portion of the left lung and throughout the right side of the chest. She was considered too ill for barium studies of the gastrointestinal tract.

On the ninth hospital day 500 cc. of whole blood was given. The white-cell count was 16,100, with 65 per cent neutrophils. During the night she was noted to be unresponsive and somewhat confused; she was slightly cyanotic and had labored respiration. On the morning of the tenth hospital day, she was deeply comatose, pale and cyanotic and had Cheyne–Stokes respiration. The blood pressure was 120 systolic, 50 diastolic. Oxygen was administered by catheter. The neck veins were not distended, and there was no evidence of vasomotor collapse. Aspiration bronchoscopy was accomplished with removal of a large amount of loose secretions. During the night she was moaning with each expiration and was in obvious distress. Bronchial breathing was heard over the left scapula and right apex. She died early in the morning of the twelfth hospital day.

DIFFERENTIAL DIAGNOSIS

DR. JOHN GORDON FREYMANN*: The "feeling of pressure high in the interscapular region" is the only mention of pain. I wonder if it persisted.

DR. DANIEL S. ELLIS: The patient was so sick that it was difficult to get a definite history from her. After admission she did complain of pain in the right scapula, which persisted.

DR. FREYMANN: Was the mild, nonproductive cough of recent onset?

DR. ELLIS: The cough was present after the onset of the chill.

DR. FREYMANN: This sixty-four-year-old woman's entire illness spanned only two and a half months from apparently good health to death, which was evidently due to respiratory failure. The onset was insidious, with nonspecific symptoms — anorexia and fatigue — and very specific symptoms, the first of which was dyspnea. There was no evidence, except for slight, nonspecific T-wave changes, of heart disease. Consequently, dyspnea of this degree must have resulted from either pulmonary disease or anemia or, more likely, both. Whenever a patient has dyspnea of this degree without cyanosis, it is entirely possible that she has a profound anemia. It is interesting that she noted the onset of hemorrhoids coincident with the onset of the disease. Certainly, hemorrhoids are not uncommon in a sixty-four-year-old woman. However, it is unusual for them suddenly to appear at this age. I assume that she did not have melena. This is not too well documented, but I think that probably the bleeding came from the hemorrhoids.

The signs and laboratory findings are of much greater help than the history. There was microscopical and completely asymptomatic hematuria, with apparently perfectly normal renal function — at least the dye was well excreted on the intravenous pyelo-

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gram, and the nonprotein nitrogen was normal. There was a very profound anemia and a nonspecific leukocytosis. I gather that there was active hematopoiesis, producing polychromasia and some variation in the size of the red cells. The indexes, I think, are generally more hindrance than help. It is unlikely that this patient had a macrocytic anemia. (Calculations show that if the red-cell count had been 2,500,000 instead of 2,300,000, the mean corpuscular volume would have fallen within the normal range.) I do not think one red-cell count provides an exact figure. It is possible, however, that she had a hypochromic anemia. The mean corpuscular hemoglobin concentration, which is based on hematocrit and hemoglobin determinations, is less inherently in error and can be trusted more than the other indexes. I hope the x-ray films will reveal the diagnosis, and I wonder if I may see them now.

DR. C. C. WANG: Two examinations of the chest were done in a period of six days. The first examination shows diffuse increase of mottled densities throughout both lung fields, somewhat more marked in the left upper lobe; the lymphatics of the right lower lung are filled with something that could be fluid or tumor (Fig. 1). The right hilar shadow is enlarged. There is also evidence of right-paratracheal-lymph-node enlargement. There is no appreciable amount of fluid in either pleural cavity. The second examination demonstrates a slight progression of the densities throughout both lung fields, particularly in the left upper lobe. The heart shadow is not unusual. No definite metastases are recognized in the bony thorax. Intravenous and retrograde pyelograms show a space-taking lesion in the lower pole of the left kidney. The right kidney may be somewhat smaller than usual, but the calyceal system appears grossly unremarkable. There is a tiny fleck of calcification in the lesion of the left kidney.

DR. FREYMANN: Is the course of the ureter normal?

DR. WANG: Yes; it is.

DR. FREYMANN: What about the filling defect in the pelvis?

DR. WANG: There is a sharply defined, smooth filling defect in the middle calyx, but actual intrinsic involvement of the renal pelvis is not evident.

DR. FREYMANN: Can you differentiate, in the roentgenogram of the chest, between miliary tuberculosis and lymphatic spread of carcinoma?

DR. WANG: I should favor the latter.

DR. FREYMANN: There are two other laboratory findings that I think should be mentioned. One is the cytologic smear of the urine, which was negative for tumor cells. When I talked to Mrs. Ruth Graham about that, she said that their batting average on a *single* examination of the urine is only about 50 per cent so that I do not think that this is helpful. The second is the fact that no blood was seen coming from the left kidney at the time of the retrograde catheterization. I do not think I have to worry about this finding because tumors of the kidney as well as tuberculous kidneys bleed intermittently.

I should like to mention two conditions, which I do not think this patient had but which should always be considered in any patient who is acutely ill and has widespread systemic involvement. The first is subacute bacterial endocarditis. Fever, an overwhelming, rapid course, leukocytosis, anemia and hematuria in an elderly patient make a good story for subacute bacterial endocarditis except for one major feature — the absence of murmurs. The spleen, which one would expect to be enlarged in subacute bacterial endocarditis, was not palpable, but I shall rule out subacute bacterial endocarditis on the absence of a murmur. Subacute bacterial endocarditis without a murmur is extremely rare, occurring in less than 1 per cent of cases.

The other disease that should also always be considered in elderly patients who become extremely sick suddenly and have widespread pulmonary changes, anemia and fever is miliary tuberculosis. This patient could perfectly well have had renal tuberculosis for many years. One ordinarily thinks of renal tuberculosis as causing painful hematuria and dysuria; however, it does not always do so. The presence of a mass in the lower pole of the left kidney is not too much in favor of renal tuberculosis although tuberculoma of the kidney can produce this picture. I cannot definitely rule out miliary tuberculosis, but there are a few things against it. When cystoscopy was performed one would expect that some degree of cystitis would have been noted and also, with the severity of this case, inflammation of the ureters. The only way tuberculosis could be ruled out definitely would be by a bone-marrow biopsy for granulomas and careful examination of the sputum and gastric contents for tubercle bacilli.

I think there is only one diagnosis that I can make in a patient with a mass in the kidney, a filling defect in the renal pelvis, painless hematuria, vague back pain, anemia and fever — that is, malignant neoplasm of the kidney. The neoplasm does not have to have been primary; it may have been secondary. Metastases to the kidneys occur but not too often. They may come from the lung, breast or pancreas and present a picture that is essentially the same as that presented by a primary malignant renal lesion. Such metastases statistically are unlikely as compared to the likelihood of a primary tumor. The lymphomas are frequently retroperitoneal in onset and sometimes never leave the retroperitoneal and mediastinal areas. When they involve the kidney the involvement is generally bilateral; they would be unlikely to produce a single lesion. On the other hand the enlarged mediastinal lymph nodes and the diffuse spread through the lung are characteristic of lymphoma. I do not think I can rule that out entirely.

Among the primary renal neoplasms are rare forms that are only of academic interest — sarcomas, neuro-

blastomas and Wilms's tumor; the last two almost always occur in infants and children but have been reported in this age group. Tumors of the renal pelvis constitute about 15 per cent of all renal cancers in this age group. They are either papillary or squamous-cell carcinomas and are highly malignant. Only 50 per cent of these occur with stones; apparently, the patient under discussion did not have stones. They frequently implant down the ureter and also invade the renal parenchyma. In view of Dr. Wang's assurance that there is no intrinsic lesion in the pelvis of the kidney, I can probably rule that out.

That brings me to the overwhelmingly most common renal malignant process in this age group, which is a renal-cell carcinoma or what we used to call hypernephroma. This has a wide spectrum of natural history from very slowly growing encapsulated tumors, which metastasize not at all or singly after many years, to highly malignant, nonencapsulated, rapidly destructive tumors, which metastasize rapidly to bone, brain and lungs. Although one thinks generally of the traditional "snowball" metastases from renal-cell carcinoma, which are hematogenous in origin, metastasis may also occur through the retroperitoneal lymphatics to the paratracheal lymph nodes and thence into the lung lymphatics. It is also well to remember that metastases may be the first manifestation of renal-cell carcinomas, and the kidney may be shown to be the primary site only when one looks for it intensively.

There are several clinical features that I have to account for. The pulmonary picture, I should say, was that of lymphatic spread of carcinoma. Probably, we cannot explain the anemia on the basis of blood loss; I do not think the patient had lost that much blood. However, the only other explanation I can bring up is that of myelophthisic anemia. One wonders if she had any bony metastases. Even though such metastases were not visible in the x-ray films there may still have been invasion of the bone marrow. Whether anemia with invasion of the bone marrow is truly myelophthisic or actually hemolytic is at present a moot point.

The hemorrhoids are an interesting manifestation; the only way I can explain them is by invasion of the venous channels in the retroperitoneal areas. Renal-cell carcinomas characteristically fungate into the renal veins and vena cava. I find it difficult, however, to visualize anatomically why with such venous invasion she would have had hemorrhoids without peripheral edema, unless the invasion occurred low in the portal tree rather than in the primary venous circulation.

My final diagnosis is renal-cell carcinoma of the left kidney, probably a granular-cell type, which tends to be more malignant, with invasion of the regional veins; metastases to the lungs via the lymphatics and possibly also by the blood vessels; metastases to the brain, which may explain the terminal coma; and probably metastases to the bone marrow, which may explain the anemia.

A PHYSICIAN: In view of the increased prothrombin time, I wonder if there were metastases to the liver as well.

DR. FREYMANN: The prothrombin time worried me, but I did not know how to relate it to the major disease. One would like to know what other liver-function tests showed. I cannot answer that.

DR. ELLIS: This patient was desperately ill from the time she came into the hospital. Without question she had been having symptoms a great deal longer than she had admitted to herself or to anyone else. When she was first admitted to the hospital the dyspnea was the most severe symptom. When I saw her that evening, I did not know about the anemia; but I believed she was dyspneic from either heart disease or anemia. The house officer, who admitted her, thought she was pale, and, of course, the hemoglobin the next morning revealed a marked anemia. From then on the questions in my mind were, Where was the blood loss and what caused the anemia? The x-ray film of the chest was interpreted as Dr. Wang suggested. We could not be sure that there was no tuberculosis. My immediate thought was to investigate the gastrointestinal tract for the source of the blood loss; when the report of the urinary findings was received we immediately investigated the urinary tract. When we established the fact that she had a lesion in the kidney, it seemed only a matter of academic interest that she might have also had a lesion in the gastrointestinal tract, and she was certainly too ill to subject to further investigation. I worried about missing tuberculosis with a tuberculoma of the kidney; however, a single smear of the sputum gave no evidence of acid-fast bacilli, and I assumed that we were dealing with widespread cancer but was not sure whether or not the kidney was the primary source. I believed that the x-ray picture was a rare one to see with renal-cell tumor, but we rode the horse of carcinoma of the kidneys, with diffuse metastases.

DR. WINFIELD S. MORGAN: I should like to ask Dr. Leadbetter whether patients may have this degree of anemia from hematuria.

DR. WYLAND F. LEADBETTER: I do not believe the anemia can be explained by the blood loss. I think Dr. Freymann's explanation is probably the correct one. I should like to ask whether he relates the fever to the primary carcinoma.

DR. FREYMANN: I think that is a very important point. Fever is sometimes the only symptom of a renal-cell carcinoma. A very interesting case of that type, presented at grand rounds about four or five years ago, was followed for weeks before renal-cell carcinoma was considered.

DR. ELLIS: This patient's fever did not respond to antibiotics. She was empirically given streptomycin and penicillin to treat any secondary infection that she may have had in the chest, but there was no change in the temperature.

DR. FREYMANN: I think anything in the retroperitoneal space can produce fever. I do not know why.

DR. LEADBETTER: One reason is necrosis in tumor. Dr. Freymann did not comment on the area of calcification in the region pointed out by the radiologist. Is that not in favor of necrosis in a tumor?

DR. FREYMANN: Calcification does occur in renal-cell carcinoma and in other kinds of tumor.

CLINICAL DIAGNOSIS

Carcinoma of left kidney, with carcinomatosis.

DR. JOHN G. FREYMANN'S DIAGNOSIS

Renal-cell carcinoma of left kidney, with widespread metastases.

ANATOMICAL DIAGNOSES

Renal-cell carcinoma of left kidney, with extension to renal veins and metastases to lungs (lymphatic spread), pleura, pericardium, liver, adrenal glands, spine and subcutaneous fat.

Adenocarcinoma of sigmoid.

PATHOLOGICAL DISCUSSION

DR. MORGAN: At autopsy there was diffuse carcinomatosis even to the presence of tumor nodules in the subcutaneous fat. The pleural cavities contained 250 cc. of straw-colored fluid bilaterally, and the surfaces were studded with tumor. The left lung weighed about 1000 gm. — twice as much as the right — and showed extensive tumor infiltration. There were a few scattered nodules measuring up to 3 cm. in diameter, but in the main the process was one of extensive lymphatic spread throughout the left lung. Tumor infiltration was less in the right lung, but both lungs showed superimposed congestion and edema.

The heart weighed 420 gm. and exhibited slight hypertrophy of the right ventricle; the pericardium was infiltrated by tumor. The liver was moderately heavy, weighing 1900 gm., and contained scattered tumor nodules up to 2.0 cm. in diameter. The pancreas and spleen were normal, and both adrenal glands contained small amounts of tumor. The spine showed extensive tumor replacement extending from the lumbar to the cervical vertebras.

The right kidney was normal; the left was twice the normal weight, and in the lower pole there was a roughly rounded, yellow and hemorrhagic, soft tumor mass showing the typical gross features of a renal-cell carcinoma. It had extended into radicles of the renal vein as well as through the capsule. Although it had deformed the calyceal system it had not extended into the calyxes, and this fact might help to explain the negative cytologic smears of the urine.

Microscopical study of some sections of the primary tumor exhibited the usual features of a renal-cell carcinoma, with vacuolated cells arranged in acini and cords, but other sections of the primary tumor and all the metastases showed a very undifferentiated type of tumor composed of large and bizarre cells, often of giant-cell proportions.

The distribution of the metastases in this case is unusual. As Dr. Freymann has pointed out, spread from a renal-cell carcinoma is most often in the form of "snowball" metastases to the lungs and not by way of a diffuse extension in pulmonary lymphatics. That type of spread is more often seen in metastatic disease from breast or stomach. I think the very malignant features observed microscopically probably explain why the metastases were so widespread. Most tumor nodules were hemorrhagic, with large areas of necrosis, — indications of very rapid growth, — and these very probably account for the fever.

In addition to all the tumor from the renal-cell carcinoma there was a localized primary adenocarcinoma of the sigmoid colon measuring about 2.5 cm. in greatest dimension. There were no apparent metastases from this, but it may well have accounted for the positive guaiac test in the stools and for some of the anemia.

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SURGEON GENERAL HOGAN

To Tufts College Medical School goes the distinction of having trained and produced the twenty-second surgeon general of the United States Navy and the first native of Massachusetts to hold this high post. Appointed to the position for a term of four years, Rear Admiral Bartholomew W. Hogan took the oath of office before the Judge Advocate General and the Secretary of the Navy on February 15, having been

nominated by the President and confirmed by the Senate.

Admiral Hogan was born in West Quincy, Massachusetts, on January 29, 1901. Educated in local schools and a graduate of Boston College High School he received his premedical instruction at Boston College and, in 1925, his degree in medicine from Tufts College Medical School. Here he was awarded the Phi Lambda Kappa Medal for highest achievement. Entering the Medical Corps of the Navy immediately on graduation, Admiral Hogan was promoted to his present rank in 1952.

Admiral Hogan, on his way to the highest position the Navy has to offer, became chief of neuropsychiatry at the Naval Hospital in Philadelphia in 1931, subsequently serving as assistant chief of neuropsychiatry at the Naval Hospital in Washington. While on this assignment he was associate professor of psychiatry at Georgetown University School of Medicine.

In March, 1942, Admiral Hogan, then a commander, reported as senior medical officer in the *USS Wasp;* he was on this duty when the ship was torpedoed and sunk in South Pacific waters on September 15 of that year. As a result of this action he

was awarded the Purple Heart, the Silver Star and the Navy and Marine Corps medals.

His citation for the Silver Star Medal read, in part:

> For conspicuous gallantry and intrepidity . . . when the (Wasp) was torpedoed by enemy Japanese submarines . . . with his carrier swept by flaming gasoline and rocked by explosions, Commander Hogan, despite his own serious wounds, worked tirelessly, caring for the injured until forced to abandon the stricken ship . . .

For the Navy and Marine Corps Medal the citation was as follows:

> For outstanding heroism . . . on September 15, 1942. Rescued from the flaming oil-covered sea by personnel of the USS Duncan, (he) in spite of serious burns on both hands and several fractured ribs, immediately took active charge of caring for the many painfully injured carried aboard the Duncan, continuing his supervision of medical attention to the more seriously wounded until the early hours of the following morning. By his unfailing loyalty, exceptional skill and outstanding devotion to duty, he contributed immeasurably to the comfort and welfare of the suffering and weary men under his care.

Admiral Hogan is a fellow of the American Medical Association, the American Psychiatric Association, the American Hospital Association and the American College of Physicians, and a diplomate of the American Board of Psychiatry and Neurology, of which he is also an examiner. In 1945 he received the honorary degree of Doctor of Laws from Mt. Saint Mary's College, Emmitsburg, Maryland, and in 1954 a similar degree, *honoris causa*, from Villanova College.

ACADEMIC SECURITY

HARD money — the funds that steadily recur year after year, whether from unfailing outside sources or from well invested capital — constitutes a type of revenue that helps the administrators of educational institutions to sleep of nights. Its persuasive lullaby is in contrast to the sweet but uncertain notes of the melody inspired by soft money — that which comes from short-term grants and other possibly or probably nonrepeating sources. The funds that are now distributed to the country's medical schools from the American Medical Education Foundation must still be considered as soft and uncertain; if they reach the equilibrium that has been achieved by many university alumni funds or twenty-five-year-class gifts, then the process of hardening can be said to be under way.

Harvard University, with its great endowments, is properly classed as one of the world's wealthiest institutions of learning, and yet, with its proportionately great responsibilities and commitments, it chronically lacks mobile funds to be directed to the points of greatest need in its many schools and relatively independent departments. Much of its hard money is too hard; unfailing though it may be, the terms under which it has been given restrict it to an unyielding function beyond the prospect of any malleability.

Hard money, then, but not brittle money, is still any university's greatest financial need, applying to Harvard as to the less well endowed institutions and applying particularly to schools of medicine, whose costs have risen out of proportion to all other branches of education. As a result of this need universities have tended to adopt for themselves standard sums for the endowment of a professorship, the income of which, in hard money, represents economic security for the incumbent of the chair.

Harvard Medical School has been especially fortunate in this respect in recent months as a result of the interest and industry of various friends of the School. The Samuel A. Levine professorship of medicine, made possible by the generosity of Mr. Charles E. Merrill, was announced in November, 1954, when only a relatively small sum was still needed to complete the endowment, and the sum being raised to endow a similar professorship in memory of Dr. George R. Minot has already reached four fifths of the required goal.

The third academic enterprise, of more recent origin, with the goal of $500,000 to be attained, is the "Stanley Cobb Fund for the Development of Teaching and Research in Psychiatry at the Harvard Medical School." This fund has an endowed chair of psychiatry in view, to be named after Dr. Cobb, so recently retired to an emeritus position in the University. Already $235,000 is in hand, although only a short time has elapsed since the project was started. Until the full amount has been raised the income from the Fund may be accumulated or may be used for the urgent needs of the Department of Psychiatry. In this way a revered educator who has been "a moving force in the development of psychiatry throughout America during his thirty-five years of teaching at the Medical School" will be fittingly recognized.

EASTER SEALS

THE Easter Seal campaign of the Bay State Society for the Crippled and Handicapped, which begins on March 10 and closes on Easter Sunday, April 10, offers an opportunity to review the Society's achievements in the ten years of its existence and also some of its activities that are of particular interest to the medical profession. It should be noted at the outset that not one cent collected during the campaign will be spent on efforts duplicating the work of any other public or private organization — reassuring information to anyone overwhelmed by the never-ending flow of worthy appeals, seasonal and nonseasonal.

In 1945 this state-wide organization was set up not only to provide adequate facilities, trained personnel and financial support for the care of handicapped children and adults but also to call public attention to their needs. A year later the Seizure Unit at the Children's Medical Center in Boston and camp vacations for crippled children had been financed. Two major projects for children with cerebral palsy, begun in

1947, have proved their worth: the Bay State Nursery School in Boston and the Bay State Treatment Training Center in Springfield. Since 1948 the Society has supported rehabilitation clinics in Worcester, Boston and Springfield, surveyed speech facilities throughout New England and extensively studied the possibility of establishing an unemployment program for handicapped persons; the last-mentioned activity at present constitutes a major goal.

This impressive record speaks for itself. The ten-year history of the Society represents a landmark in progress toward the solution of a crucial social and economic problem: the rehabilitation and return to gainful employment of patients formerly considered a burden to themselves and their fellows. The rewards of such a program are great, not only to the crippled person and his family but also to society, which may thus be able to exchange a welfare charge for a productive citizen. The Easter Seal campaign, which is the only source of income for this vital service to the Commonwealth, merits the enthusiastic and generous support of all who believe that disability need not entail individual idleness and incapacity or a burden on the community.

FOND MEMORY

For something over twenty-seven years, or since October 20, 1927, the *Journal* has been the official publication of the New Hampshire Medical Society. At the time when the arrangement was made the publication still operated under its title of longest standing, — that of the *Boston Medical and Surgical Journal*, — assuming its present designation in February of the following year.

The *Journal* had already become the official organ of the Massachusetts Medical Society in 1914 and of the New England Surgical Society in 1916; and in 1921, the same year in which the Massachusetts Medical Society became its proud proprietor, it became also the voice of the Boston Surgical Society, Incorporated. Further liaisons followed in orderly procession. The New England Pediatric Society entered the alliance in 1924, and the Vermont State Medical Society in 1928, and in the 1930's the New England Obstetrical and Gynecological Society and the Neisserian Medical Society of Massachusetts, an organization devoted to moral uplift as well as to medical improvement, came into the fold.

Brave beginnings, however, did not ensure a continuity of effort, and with changing officers and shifting memberships interests often lagged. By 1940 only the New Hampshire and Vermont societies remained on the roster of those organizations that seemed eager to claim the glad distinction of having the *New England Journal of Medicine* as their official organ, and the Vermont Society maintained the relations barely into 1941.

For thirteen more years, as the *Journal* entered its period of most substantial expansion, the New Hampshire Society held to its status, but with a diminishing employment of the *Journal's* facilities and under an arrangement — that of subscribing for its members to only one issue of the *Journal* each month — that was hardly designed to increase their interest in the publication as a whole. The delegates of the New Hampshire Society have therefore voted to discontinue the friendly official association of nearly a generation's duration, but "to continue a voluntary cooperative contact with the *Journal* staff."

Probably an important factor in the abandonment of an official organ status by the various societies has hinged on the publication of papers read at their meetings. The editors of the *Journal* have long held that papers submitted for publication must be judged on their merits alone and that many worthy platform addresses are not suitable for perpetuation in the printed annals of medicine.

The editors of the *Journal*, who have believed for some time that the once-a-month subscription was entirely satisfactory to no one, have approved of the separation, in the belief that the New Hampshire Society can profit even more from a less formal arrangement. At this almost imperceptible divergence of the ways, they wish to emphasize their desire to be of continuing service to the professional brethren of a sister state.

The eighth Annual Meeting of the American Medical Association will be held in the city of Philadelphia on Tuesday, May 1, 1855.
Boston M. & S. J., *March 22, 1855*

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Georgetown University School of Medicine, 1953.
WALLACE, GEORGE, 119 Belmont Street, Worcester.
Chicago Medical School, 1944. Sponsor: Dr. Bancroft C. Wheeler, 27 Elm Street, Worcester.
WEIDEMANN, KARL C., 286 Lincoln Street, Worcester.
University of Frankfurt, 1944. Sponsor: Dr. Elwood Horne, 286 Lincoln Street, Worcester.

Burte Guterman, M.D., *Secretary*
16 Norwich Street, Worcester

DEATHS

CURLEY — John J. Curley, M.D., of Leominster, died recently. He was in his fifty-sixth year.

Dr. Curley received his degree from Tufts College Medical School in 1922. He was chief of staff, Leominster Hospital, and medical examiner for North Worcester County, a member of the New England Obstetrical and Gynecological Society and a fellow of the American Medical Association.

He is survived by his widow, a daughter and two sons.

HARTWELL — Arthur S. Hartwell, M.D., of Norwood, died on February 26. He was in his eighty-sixth year.

Dr. Hartwell received his degree from Jefferson Medical College of Philadelphia in 1897. He was one of the founders of the Norwood Hospital, a fellow of the American College of Surgeons and, formerly, medical examiner for Norfolk County.

He is survived by a daughter.

ROMBERG — Eli C. Romberg, M.D., of Brookline, died on February 28. He was in his sixty-fourth year.

Dr. Romberg received his degree from Harvard Medical School in 1920. He was a member of the staffs of the Massachusetts General and Beth Israel hospitals, New England Pediatric Society and Massachusetts Physicians Art Society and was a founder of the Phi Delta Epsilon Fraternity.

He is survived by his widow, a daughter, a son and two sisters.

CORRESPONDENCE

REGARDING TRANQUILITY

To the Editor: As usual the *Journal* is up to date with its comments, and I read with interest the leading editorial in the January 13 issue entitled "Tranquilizing Agents." These new drugs are very *exciting* to many physicians who use them.

I would, however, take exception with the use of the term "tranquilizing" to describe the action of the two drugs, reserpine and chlorpromazine. Any drug that "slows pulse rate, lowers blood pressure and calms excited and agitated patients" is best described as a sedative, and I think it is well to use this term since it is well understood in the medical literature. The unusual feature about reserpine is that it does frequently give good sedation without the hypnotic effect and is thus superior to phenobarbital. The term "tranquilizing" has no particular meaning and to introduce such a term in the medical literature seems to me to be both unnecessary and unwise. Could it be that the conservative *New England Journal of Medicine* has been influenced unduly by the many advertisements that have appeared on its pages in which the term "tranquilizing" has been used? The use of such a term may be good business, but it is poor medicine.

I should also like to question the explanation for the undesirable effect these drugs occasionally have on some people. To say that the undesirable agitated feeling that occasionally results from both reserpine and chlorpromazine "is the refusal of certain persons to submit to the tranquilizing effect" seems to me to be both hypothetical and unsound. It is an observed fact that a common drug like morphine produces stimulation in some people, whereas in most it has a soothing, quieting, analgesic effect.

I trust that this letter does not disturb your usual calm and peaceful state of mind.

JAMES H. CURRENS, M.D.

Boston

REGARDING REPRINTS

To the Editor: I have much sympathy with the ideas expressed in the editorial entitled "Requests for Reprints," which appeared in the December 16 issue of the *Journal*. I am a fairly prolific writer and find that for each article I need 100 to 150 reprints for distribution to those who request them. Some I receive free, but on the average I spend about $9, with postage up to $4, for each article published. Fortunately, I do not have to bear the full costs, but I have great sympathy with those who do. If I did not have to distribute reprints, I should arrange to have microfilm copies of the articles that interest me at a cost of about 2½ cents a page and even if I had to buy a microfilm reader, I should save money.

Though I regard the reprint collector with some distaste, I think that reprints are valuable especially for persons in countries other than that of the author. Often, the original journal is difficult to obtain, and yet the contents of the article deserve the most detailed study. The proposals advanced in the editorial would make it easy for one's co-nationals but difficult for foreigners to obtain reprints of valuable papers, for many countries, including my own, still maintain some form of exchange control, and to pay many small bills in United States currency would drive me, my bankers and the exchange control to distraction; nor do I know how much American publishers would enjoy opening thousands of new small accounts, many of which would be with practitioners on the other side of the Atlantic and behind the Iron Curtain. I fear that the proposals would limit the exchange of ideas between nations.

For my part, I impose a self-denying ordinance, which I think should be generally adopted: not to request reprints from my co-nationals. My British colleagues rarely ask me for reprints. I receive from and send to the United States most of the reprint request cards, but of late there has been an increasing exchange with Western and Eastern Germany, Czechoslovakia, Hungary, Spain, Argentina and Brazil; I believe that I should continue this exchange.

I think that reprint exchanges should die, but not until every country has proper facilities for microfilm copying, nor until the copyright laws have been revised.

GEORGE DISCOMBE

London, England

HE WHO LAUGHS LAST LAUGHS LAST

To the Editor: I read, with a great deal of interest, the editorial "Ring Out, Wild Bells" in the February 10 issue of the *Journal*. Unfortunately, I found myself confused by

the calendar. Out here, west of Worcester, all our weeks are of the same length and begin on the same day.

We use a rather old book out here as our arbiter (" . . . and on the seventh day He rested"). I imagine this book to be scarce in the Hub of the Universe. I know that in the past copies have even been pilfered from the rectory libraries.

Is "The Direct Mail Advertising Association, Incorporated" a Boston institution like the Athenaeum or Swan Boats, or is this change of calendar from some other heathen city east of the Hudson?

We await your answer here in Ann Arbor with trepidation lest we have been using the wrong book in deciding the length of our weeks.

JOHN B. STETSON, M.D.

Ann Arbor, Michigan

Note: The *Newsletter* of the Direct Mail Advertising Association, Incorporated, is published in New York City, a municipal congeries approximately East by Southeast of Ann Arbor, Michigan. The six-day weeks noted by Dr. Stetson are possibly the result of consulting that Book (probably borrowed in Boston) that sets aside the seventh day as one of rest. No references are available giving any authority for nine-day weeks, and it is a source of local comfort that no responsibility for such irregularities can be placed in Boston.

Dr. Stetson will be interested to learn that, according to a more recent newsletter of DMAA, all March has been set aside as One-Dish Meals with Cheese Month, March 6 to 12 as National Peanut Week, and March 27 to April 2 as National Laugh Week.—ED.

BOOK REVIEWS

Neurosurgery of Infancy and Childhood. By Franc D. Ingraham, M.D., associate professor of surgery, Harvard Medical School, neurosurgeon-in-chief, Children's Medical Center, neurologic surgeon, Peter Bent Brigham Hospital, Boston; and Donald D. Matson, M.D., assistant professor of surgery, Harvard Medical School, neurosurgeon, Children's Medical Center, senior associate in neurologic surgery, Peter Bent Brigham Hospital, Boston. 4°, cloth, 456 pp., with 482 illustrations. Springfield, Illinois: Charles C Thomas, 1954. $15.00.

The authors have had an unusually large experience in handling neurologic disorders amenable to surgery at the Children's Medical Center and the Peter Bent Brigham Hospital in Boston. The book reflects their personal encounters with many trying conditions, such as the wide variety of congenital malformations of the spinal cord and the brain and its coverings. In this field they offer most help, for the more general conditions, such as acute and chronic trauma, inflammation and tumors, when found in children, do not present problems differing markedly from those found in adults and already adequately covered by many books on neurosurgery. Over 150 pages are therefore devoted to the subjects of congenital anomalies and hydrocephalus, and this section gives the book a unique place in the field of medical literature. Operative technic is competently described and there is a special chapter on pediatric neurosurgical anesthesia. The illustrations call for special commendation, and the whole book sets a standard in the best traditions established in the past at the same hospital by Harvey Cushing.

HENRY R. VIETS, M.D.

The Physician and His Practice. Edited by Joseph Garland, M.D., editor, *New England Journal of Medicine.* 8°, cloth, 270 pp., with illustrations. Boston: Little, Brown and Company, 1954. $5.00.

Dr. Garland has collected and edited an interesting and valuable collection of papers designed for the use and information of the young physician just beginning practice. Eighteen persons — physicians, lawyers and others — contributed to the volume. The important business side of medicine is considered, with discussions on accounting practices and the income tax, the office and its management and related business aspects, assistants and employees, and the keeping of proper records. A lawyer deals with medicine and the law. Emphasis is given to family and community relations and the place of the doctor's wife in these relations. There are a number of articles on the practice of medicine and the selection of a field of practice and on national and community resources. There is a chapter on reading and writing, with sound advice. A lawyer contributes a valuable article on economic security, discussing at length investments, insurance — life, health, accident, liability (malpractice) — and property, wills and trusts and tax savings.

To review the contents of this volume in detail would require another small book. This is an important book that should be in the libraries of all young physicians and should prove valuable to all physicians.

JAMES F. BALLARD

Studies in Schizophrenia: A multidisciplinary approach to mind-brain relationships. By the Tulane Department of Psychiatry and Neurology. Reported by Robert G. Heath, chairman. 8°, cloth, 619 pp., with illustrations. Cambridge, Massachusetts: Harvard University Press, 1954. (Published for the Commonwealth Fund.) $8.50.

This impressive volume represents the combined labors of twenty-two workers in the Tulane Department of Psychiatry and Neurology. It is remarkably complete over all and interestingly technical in some sections, particularly that concerning technic, which is Dr. Heath's particular contribution to this study.

Schizophrenia, whatever it may be, is still an unsolved problem of major importance in the treatment of mental illness. This book is particularly broad and illuminating in its many applications of various technics and approaches to this problem. Although the central idea is well described in the subtitle much credit should be given the inspired and persistent efforts of Dr. Heath, who brought together a remarkable collection of participants to apply and appraise his animal studies and the results obtained from observations of human beings in whose brains subcortical electrodes had been implanted. This book contains so many valuable psychologic data, case reports, outlines of histories and discussions that it will take a reasonable amount of time for its full impact to reach the medical profession, but as it stands, it will appeal equally to psychiatrists, neurosurgeons, research workers and therapists. It is more than a monograph — it is a compendium particularly representing the value of teamwork in attempting to solve the major problem in psychiatry that to date has defied solution. The psychiatrists who can truly show definite progress toward defining and definitely dealing with schizophrenia will deserve more than the Nobel Prize; they will merit a cluster of them. And when that day comes, it will probably not be an individual who cracks this hardest of all nuts but a group effort, probably a group like the one whose efforts are described in this book, which the Commonwealth Fund and Harvard University Press have seen fit to publish so painstakingly.

MERRILL MOORE, M.D.

The Thyroid. A Physiological, Pathological, Clinical and Surgical Study. By T. Levitt, M.A., F.R.C.S. (Eng.), F.R.C.S. (Ed.), F.R.C.S.I., Hunterian Professor of the Royal College of Surgeons of England, lecturer in surgery to the Fellowship of Post-graduate Medicine at the New End Hospital, Hampstead, London, sometime surgeon, Paddington Hospital, London, first surgical assistant, Thyroid Clinic, New End Hospital, London, and demonstrator in anatomy, Middlesex Hospital, University of London. 8°, cloth, 606 pp., with 501 illustrations and 153 tables. London: E. and S. Livingstone, Limited, 1954. $20.00.

The author has been one of the leaders in the field of thyroid disease for more than twenty-five years, and his book is based on 2000 consecutive thyroidectomies done in London and provincial hospitals. His first chapters deal with the natural history of thyroid disease, and subsequently he treats the clinical manifestations, diagnosis and various means of treatment, including surgery and radioactive iodine. Detailed operative technic is described and illustrated by draw-

ings, photographs, charts and a wealth of pictures, many of them sumptuously produced in color. The greatest part of the work is original, with the author's opinion on difficult and perplexing problems fully presented. A new nomenclature has been introduced, and an appendix includes translations of Riedel's three original contributions (1896, 1897 and 1910), as well as Hashimoto's paper (1912). A provocative and inspiring book, finely printed and produced, Levitt's monograph sets a high standard in literature on the thyroid gland.

HENRY R. VIETS, M.D.

Psychomotor Aspects of Mental Disease: An experimental study. By H. E. King. Cambridge, Massachusetts, published for the Commonwealth Fund by Harvard University Press, 1954. 8°, 185 pp. $3.50.

This book is a report of an experiment in which the performance of 194 normal subjects on four psychomotor tests was compared with that of 90 hospitalized patients with chronic schizophrenia and 50 outpatients with subacute behavior disorders. The tests, three of which were selected on the basis of prior factor analyses, were as follows: a simple reaction-time situation, in which the response was the pressing of a telegraph key placed 27 cm. away from a starting position; a complex reaction-time test with similar responses; a tapping test in which the subject alternately touched two plates 30 cm. apart as fast as he could for five seconds; and a finger-dexterity test, the Purdue Pegboard. Seven measures in all were obtained, two from each test, except the tapping test. On the seven measures the mean performance of the patients with chronic schizophrenia was roughly 50 per cent of the normal value, and that of the outpatient group about 88 per cent of the same value. The schizophrenic persons, further subdivided into three groups on the basis of different sets of judgments, showed deterioration in performance in accordance with the deterioration judged according to the three scales. Similarly, in the outpatient group, divided into two subgroups, the more severe cases showed a greater psychomotor deficit.

Two general ideas are advanced to explain the faulty performance of the mentally ill: that it is a secondary reflection of a general withdrawal or negativism; and that it is a "primary indication of disturbance in a basic adaptional process, that of motor adjustment to the external surround." Perhaps an analysis of the data of each chronic patient in terms of the judgments made about his co-operation, willingness, grasp of instructions, effort and attention in the test situation would have been profitably used to elucidate the actual scores.

In general the work is well reported. However, there are a few unfortunate misprints — for example, three in the sample record of a chronic patient. The use of thousandths of a second to describe the beginning of a single response and of hundredths of a second to indicate the end of the same response is annoying. However, the positive findings are remarkable, and further work of this sort should certainly be welcomed.

JOHN P. FLYNN, Ph.D.

BOOK RECEIVED

The receipt of the following book is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Painful Phantom: Psychology, physiology and treatment. By Lawrence C. Kolb, M.D., Section of Psychiatry, Mayo Clinic, Rochester, Minnesota. 8°, paper, 50 pp., Springfield, Illinois: Charles C Thomas, 1954. $1.50. (Publication No. 235, *American Lecture Series.)*

This study of pain in nonexisting extremities is based on two operations — prefrontal lobotomy and amputation. Two illustrative cases are presented in detail, and the literature is surveyed. There is a list of 38 references.

NOTICES

PHI DELTA EPSILON FRATERNITY GRADUATE CLUB OF BOSTON

The annual convention and dinner dance of the Phi Delta Epsilon Fraternity Graduate Club of Boston will be held at the Somerset Hotel, Boston, on April 30. Information may be obtained from Dr. Edward L. Zarsky, 422 Beacon Street, Boston.

BOSTON STATE HOSPITAL

PSYCHIATRY SEMINARS

The schedule for the psychiatry seminars of the Boston State Hospital, to be held in the reception-building auditorium at 11 a.m., is as follows:

March 30. Research in Rehabilitation. Dr. Ralph Notman.
April 6. The Resistive Relative. Mr. Robert Mulford.
April 13. Progress in Psychiatric Nursing. To be announced.
April 20. Reflections on the Concept of Maturity in Personality. Dr. Robert W. White.
April 27. Conscience and Mental Health. Rt. Rev. Thomas J. Riley.
May 4. Progress in Psychiatric Rehabilitation. Dr. Maxwell Jones.
May 18. The Danger of Suicide. Dr. William F. Murphy.
May 25. Blood Diseases in a Mental Hospital. Dr. William Dameshek.
June 1. The Place of Electroencephalography in Mental-Hospital Practice. Dr. Milton Greenblatt.
June 8. Short-Term Psychotherapy. Dr. Greta L. Bibring.
June 15. Bone and Joint Problems in Mental-Hospital Practice. Dr. Richard A. Bragdon.

LAHEY CLINIC LECTURES

The Lahey Clinic lectures will be given in the Joslin Auditorium, New England Deaconess Hospital, from 7:30-9:00 p.m. as follows:

April 6. Management of Facial Paralysis. Dr. Frank D. Lathrop.
Diagnosis and Management of the Commonest Ear, Nose and Throat Complaints. Dr. G. David King.
April 13. Diseases of the Pituitary Gland.
Present Concepts of the Growth Hormone. Dr. Lewis M. Hurxthal.
Physiology and Disturbances of Ovarian Function. Dr. A. S. Parker.
April 20. Fluid and Electrolyte Balance. Dr. George Bell.
April 27. Breast Tumors. Drs. Cornelius E. Sedgwick, Ferdinand Salzman and William Meissner.
May 4. Anaphylactic Shock in Medicine and Surgery. Drs. John Fromer and J. J. Goodman.
May 11. Surgery of Tuberculosis. Dr. Norman Wilson.
May 18. Management of the Leukemic Patient. Dr. John W. Norcross.
The Bleeding Dyscrasias. Dr. Donat Cyr.
May 25. Treatment of Diabetic Feet. Dr. John McKittrick.

MASSACHUSETTS STATE SOCIETY OF MEDICAL TECHNOLOGISTS

The annual spring meeting of the Massachusetts State Society of Medical Technologists will be held at the Hotel Sheraton Plaza, Boston, on April 23. Further information may be obtained from Beverly Balch, Blood Grouping Laboratory, 332 Longwood Avenue, Boston.

MASSACHUSETTS SOCIETY OF EXAMINING PHYSICIANS

The annual meeting of the Massachusetts Society of Examining Physicians will be held at the Harvard Club, Boston, on March 23, starting with the social hour at 6:00 p.m.

Dr. Robert T. McElvenny, associate professor of bone and joint surgery, Northwestern University Medical School, will speak on the topic "The Rise and Decline of Medical Expense and Hospital Costs." All members of the Massachusetts Hospital Association are invited.

AMERICAN TRUDEAU SOCIETY

The fiftieth-anniversary meeting of the American Trudeau Society, medical section of the National Tuberculosis Association, will be held in conjunction with the annual meeting of the National Tuberculosis Association in the Milwaukee Auditorium, Milwaukee, Wisconsin, May 23 - 27.

Discussions will concern the chemotherapy of tuberculosis and other medical aspects of treatment, surgical management of tuberculosis and related diseases and current research in tuberculosis.

STUDENT AMERICAN MEDICAL ASSOCIATION

The fifth annual convention of the Student American Medical Association will be held at the Sherman Hotel, Chicago, May 6 - 8.

An address entitled "Medicine and Diplomacy" will be delivered by Dr. You Chan Yang, Korean ambassador to the United States, and Dr. Louis J. Regan will participate in a panel on forensic medicine. All members of the medical profession are invited.

AMERICAN ASSOCIATION FOR CLEFT PALATE REHABILITATION

The thirteenth annual meeting of the American Association for Cleft Palate Rehabilitation will be held at the Statler Hotel, Boston, May 13 and 14. Persons interested in presenting papers or organizing symposiums should write to Dr. Alex Fox, 1653 Main Street, Springfield, Massachusetts.

AMERICAN COLLEGE OF ALLERGISTS

The eleventh annual congress and graduate instructional courses in allergy of the American College of Allergists will be held at the Morrison Hotel, Chicago, April 25 - 30. The annual oration will be delivered by Dr. Robert A. Cooke on the topic "Medical Research in the Field of Allergy." Further information may be obtained from the American College of Allergists, La Salle Medical Building, Minneapolis 2, Minnesota.

SOCIETY MEETINGS AND CONFERENCES

March–April. Postgraduate Medical Institute. Page 451, issue of September 9.
March–May. Sanitary Engineering Center Training Programs. Page 122, issue of July 15.
March 21–23. Aero Medical Association. Page 371, issue of March 3.
March 21–April 18. Hartford Medical Society. Page 289, issue of February 17.
March 22. Norfolk District Medical Society. Page 371, issue of March 3.
March 23. Massachusetts Society of Examining Physicians. Notice above.
March 23–26. International Academy of Proctology. Page 876, issue of November 18.
March 24–30. Consultation Clinics for Crippled Children in Massachusetts. Page 328, issue of February 24.
March 25. Postgraduate Course in Occupational Medicine. Page 922, issue of November 25.
March 28. Massachusetts Heart Association (Kidney Section). Page 414, issue of March 10.
March 30–June 15. Boston State Hospital. Psychiatry Seminars. Page 461.
April 1. American Psychiatric Association (Massachusetts District Branch). Page 289, issue of February 17.
April 1. New England Society of Anesthesiologists. Page 289, issue of February 17.
April 2–May 7. Middlesex South District Medical Society. Postgraduate Course. Page 758, issue of October 28.
April 5. Microcirculatory Conference. Page 289, issue of February 17.
April 6 and 7. American Heart Association. Page 371, issue of March 3.
April 6–May 25. Lahey Clinic Lectures. Page 461.
April 7–9. Postgraduate Course in Obstetrics and Pediatrics. Page 329, issue of February 24.
April 8. Massachusetts Society for Research in Psychiatry. Page 679, issue of October 14.
April 13. Chelsea Soldiers' Home. Page 329, issue of February 24.
April 15. New England Surgical Society. Spring Meeting. Massachusetts Memorial Hospitals and Boston University School of Medicine.
April 21 and 22. New York Academy of Medicine (Eastern States Health-Education Conference). Page 922, issue of November 25.
April 23. Massachusetts State Society of Medical Technologists. Page 461.
April 25–30. American College of Allergists. Notice above.
April 28–30. American Goiter Association. Page 329, issue of February 24.
April 30. State University College of Medicine at New York City. Page 289, issue of February 17.
April 30. Phi Delta Epsilon Fraternity. Graduate Club of Boston. Page 461.
May 4 and 5. American Psychosomatic Society. Page 286, issue of August 12.
May 6–8. Student American Medical Association. Notice above.
May 13 and 14. American Association for Cleft Palate Rehabilitation. Notice above.
May 17–19. Massachusetts Medical Society. Annual Meeting. Hotel Statler, Boston.
May 18–20. American College of Cardiology. Page 414, issue of March 10.
May 23–27. American Trudeau Society. Notice above.
June 5 and 6. American Board of Physical Medicine and Rehabilitation. Page 794, issue of November 4.
June 21–25. National Association for the Prevention of Tuberculosis. Page 540, issue of March 25.
August 28–September 2. American Congress of Physical Medicine and Rehabilitation. Page 157, issue of January 27.
October 23–27. American Institute of Dental Medicine. Page 414, issue of March 10.
November 6–13. Second International Congress of Allergology. Page 157, issue of January 27.
November 19–21. American Association of Blood Banks. 8th Annual Meeting. Palmer House, Chicago, Illinois.
November 29–December 2. Interim Session of the American Medical Association. Boston.

Calendar for the Week Beginning Thursday, March 24

Thursday, March 24

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*9:00–10:00 a.m. Grand Rounds. Russell Room, House of the Good Samaritan.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–1:00 p.m. Thoracic Conference. Esophageal Lesions. Drs. Merrill C. Sosman, Alexander W. MacMillan, Jr., and Dwight E. Harken. Main Amphitheater, Peter Bent Brigham Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital, Cambridge.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
*4:00–5:00 p.m. Pediatric Seminar. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.

Friday, March 25

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by a Member of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
11:00 a.m. Mortality and Morbidity Meeting. Dr. James J. Meehan, presiding. St. Margaret's Hospital, Dorchester.
*11:00 a.m.–1:00 p.m. Medical Grand Rounds. Dr. Proger and Staff. Stearns Auditorium, New England Center Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*4:00–5:00 p.m. Child Psychiatry. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*4:00–6:00 p.m. X-Ray Conference. Dr. Merrill Sosman. Stearns Auditorium, New England Center Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.

(Concluded on page xxxi)